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WORLD CONGRESS

THE PARTICIPANTS in the Second World Congress of Anaesthesiologists have dispersed to the four corners of the globe, each to his daily round of service in the practice of anaesthesia. Each and every one of these must at some time reflect on the Congress and its meaning for him. For some, the great experience may have been the opportunity to visit a new continent, a new country, a new people. Others may have had the satisfaction of meeting "great names" in the specialty, and the pleasure of finding that these names belonged to kindly and unassuming human beings. For the traveller of yesterday there was the opportunity once again to renew old friendships, and to make new friends.

Transcending all other experiences of the Congress, however, was the sharing of knowledge through the presentation and thoughtful discussion, by experts from many lands, of the scientific basis and clinical applications of anaesthesia. No number of printed words can ever equal in value even a few brief hours of such discussion. In such an exchange undoubtedly the seeds have been sown for much future progress in anaesthesia, to the ultimate benefit of mankind.

We venture to predict that the lasting monument to the World Congresses of Anaesthesiologists, both past and future, will be increased knowledge and mutual understanding and respect amongst the anaesthetists of our world, and better anaesthesia for all the people of the world.

"NEW ERA"

WITH THE PUBLICATION of this issue, the Journal enters a new stage of development. The current volume will be published in six issues, appearing bi-monthly. It is the hope of the Editorial Board that the new policy of more frequent publication will reduce the delay between receipt of communications and their appearance in print—a factor which has in the past proved frustrating both for contributors and for the Editor.

CONGRÈS MONDIAL

LES CONFRÈRES qui ont assisté au Deuxième Congrès mondial des Anesthésiologistes sont maintenant dispersés aux quatre coins du monde, chacun étant occupé à la besogne quotidienne de son service et pratiquant l'anesthésie. Tous et chacun d'eux, à l'occasion, doivent se rappeler ce Congrès et son importance pour chacun. Pour les uns, il est possible que la plus grande expérience ait été l'opportunité de visiter un nouveau continent, un nouveau pays, un nouveau peuple. Pour d'autres, le plus grand plaisir, au cours du congrès, peut avoir consisté en la rencontre de "grands personnages" de la spécialité et en la découverte que ces individus sont des humains pleins de bonté et sans prétention. Pour le voyageur d'hier, c'était une nouvelle opportunité de renouer d'anciennes amitiés et de se faire de nouveaux amis.

Cependant, au-dessus de toutes les autres expériences du Congrès, il y avait le partage des connaissances scientifiques par la présentation et la discussion judicieuse, par des experts de plusieurs pays, des bases scientifiques et des applications cliniques de l'anesthésie. Un nombre illimité de termes imprimés ne peuvent pas avoir la valeur de quelques brèves heures de semblable discussion. Avec de tels échanges, il n'y a pas de doute que des grains de semence ont été mis en terre pour donner naissance à de grands progrès futurs en anesthésie pour le bienfait ultime du genre humain.

Nous osons prédire que ce qui survivra du congrès mondial des anesthésiologistes, aussi bien du passé que de celui à venir, ce sera une connaissance accrue et une entente et un respect mutuels entre les anesthésistes de notre monde—puis une meilleure anesthésie pour tous les gens du monde.

"ERE NOUVELLE"

AVEC LA PUBLICATION de ce numéro, le journal entre dans une nouvelle phase de développement. Le volume actuel va être publié en six numéros, un apparaissant à tous les deux mois. Les éditeurs nourrissent l'espoir que cette nouvelle initiative de publier plus souvent réduira le délai entre la réception des communiqués et leur publication; ce fait, dans le passé, s'est avéré gênant aussi bien pour les auteurs que pour les éditeurs.

PARANATAL ANOXIA AND ITS RESIDUAL ENCEPHALIC LESIONS*†

CYRIL B. COURVILLE, M.D.‡

And a certain man lame from his mother's womb was carried, whom they laid daily in the gate of the temple which is called beautiful, to ask alms of them that entered into the temple.

ACTS 3:2

THIS BRIEF MENTION of a man crippled in his lower extremities who, according to St. Luke, the physician, was "lame from (his) mother's womb", constitutes a historical introduction to the concept of the serious effects of abnormal birth. The specific cause of such disabilities seems to be echoed in a statement made centuries later by one William Little[2] who wrote: "In two cases, the birth occurred at the full period of gestation, but owing to the difficulty and slowness of parturition, the individuals were born in a state of asphyxia (asphyxia neonatorum), resuscitation having been obtained at the expiration of two and four hours through persevering efforts of the accoucheurs." Over the long period which has elapsed between the pronouncements of Saint Luke and "Saint" Little, it has come to be recognized that children who have been crippled "from their mother's womb" may develop "permanent spastic contractions in various parts of the body."§ Moreover, from the time that such deformities were first painted on the walls of Egyptian sepulchres, depicted on the canvasses of mediaeval masters, and described by medical writers since the Renaissance, the clinical picture of these deformed individuals has become indelibly impressed upon the hearts and minds of laymen and physicians alike.

The reason for this tardiness on the part of medical historians in connecting the occurrence of paranatal asphyxia and the development of the several forms of paralytic phenomena results from a failure to comprehend the complex mechanism of anoxia. It is true that Little's contemporaries were willing to designate spastic paraplegia as "Little's disease," but the precise relationship

*Much of the investigative work on which the present survey is based has been aided by a grant (B-1248) from the National Institute of Neurological Diseases and Blindness, Bethesda, Maryland.

†In order to avoid confusion, the terms hypoxia and anoxia are used in the sense suggested by Wiggers.[1] Accordingly, hypoxia implies a lowered oxygen tension in the blood resulting in physiological changes which are reversible leading to complete normalcy; anoxia indicates a state of oxygen lack to a degree resulting in pathological alterations in the brain followed by either fatal issue or physical and/or mental deficits during the survival period.

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§The clear understanding of William Little in this matter of the relation between paranatal anoxia and certain deformities of the extremities has now become so widely recognized that his name should certainly be suggested for early canonization among the "saints" of medical science.

between the anoxic cause and deforming motor effect was overlooked. The entire problem was subsequently thrown into a turmoil by the variable picture of the cerebral lesions found at autopsy in these cases. Moreover, the convincing pronouncements of such authorities as Osler[3] and Freud[4] were misleading to their contemporaries. Although they were not certain as to the precise cause of this brain damage, they had decided that it was not due to asphyxia. Living in 1960, we cannot so readily be excused for our ignorance; a quarter of a century has now elapsed since the effects of anoxia of the human brain have become known. In the light of present-day knowledge, it is therefore fair to ask why medical writers still persist in designating these natal episodes as "birth injuries." Because the motor and intellectual residuals of the anaesthetic anoxias, for example, are so definitely recognized, why are we so slow to acknowledge their clinical counterparts in children who have experienced a severe degree of anoxia at the time of birth? Now that we can readily identify post-anoxic changes in the brain of adults, why are neuropathologists in particular so reluctant to admit the same lesion in the brain of a child, damage which obviously dates back to the birth process?

In this brief presentation, the writer hopes to make clear to anaesthetists, so vitally concerned with the effects on the brain of oxygen deficiency, the true status of this problem. If it is true, as Beecher and Todd[5] have suggested, that the most common complication of anaesthesia is still cerebral anoxia, every well-trained anaesthetist is without excuse on this point.

Importance of Paranatal Anoxia to Present-Day Medicine

It is legitimate to inquire "Just how important are the residuals of paranatal anoxia to present-day medicine? Does it have a possible answer to some questions as to the still unsolved etiology of certain neurological or psychiatric disorders, or is the entire matter 'much ado about nothing'?" The most direct approach to the answer of this question is to evaluate briefly the three major symptoms of anoxia that occur in our post-anaesthetic hypoxic patients.

These symptoms are (i) the hyperkinetic phenomena such as muscle tremors, jerkings, and most of all true convulsive seizures, (ii) paralytic manifestations in the more severely affected individuals, and (iii) the intellectual obtuseness, emotional aberrations, and behaviour disorders.*

In the first place, the problem of *epilepsy* assumes medical importance if for no other reason than its frequency. If the group of convulsive disorders that date back to the time of early infancy or to birth itself are investigated, it will be found that these phenomena include a variety of disorders which are usually associated with a generalized cerebral dysrhythmia as noted on the electroencephalogram. Do these "spells" have any causal relationship to an anoxic process occurring during birth? When such convulsive attacks occur in cases of cerebral palsy in association with characteristic anoxic lesions in the brain,

*If indeed these are the acute and subacute effects of post-anaesthetic anoxia, why should we be surprised that epilepsy, palsy, or intellectual deficits can be consequences of the chronic post-anoxic state?

there can be but little question. In such instances, it is logical to assume that both the palsied state and the convulsive seizures are due to the single etiological factor of anoxia.

There can also be little uncertainty in cases in which the seizures have occurred since early infancy but are either purely jacksonian in nature or are generalized with constant localizing manifestations associated with corresponding focal electroencephalographic dysrhythmias. So often, a surgical exploration results in the disclosure of focal cortical scars or cysts. Such lesions have been described by Ford[6] and Penfield and Erickson.[7] Microscopically, their structural characteristics indicate an identity with more recent anoxic alterations of later life.

The greatest degree of uncertainty exists as to whether there is any causal relationship between paranatal anoxia and the so-called "idiopathic" convulsions. In these instances, it is not often that one can elicit a clear-cut history of a paranatal anoxic state. Even the occurrence of an apnoeic state is frequently not recalled by the mother. There is some indirect evidence, however, that may have a significant bearing on this point. Nielsen[8] and subsequently Nielsen and Butler[9] pointed out that the first child born to a given family has a much greater likelihood of developing convulsive seizures. This correlates with the well-known fact that it is the first born child which is most apt to have difficulty in the birth process. In a subsequent study, Nielsen and Courville[10] reviewed the evidence favouring the possibility that many cases of epilepsy do have their genesis in anoxia at birth. It is also likely that in many such instances, any clinical evidence of anoxia may not have been observed, but it is now known that this state may exist in a cryptic form as a circulatory disorder. There is a strong suspicion on the part of the present writer that oversedation of the mother may play an important role in this process.[11] This point will be considered further in a subsequent section.

There is certainly much need for careful clinical studies of the total birth picture in idiopathic epilepsy, particularly with respect to evidence of foetal distress *in utero* and the amount of sedation given in relation to the period of apnoea together with the determination of the oxygen content of the blood in the umbilical vessels during the process of delivery.

The matter of *deficiencies in the intellectual field* should also be given critical scrutiny from this viewpoint. A review of a series of cases of cerebral palsy has shown that in from 30 to 40 per cent some degree of impaired mentation occurs.[12] It is not difficult in such cases with serious brain lesions to understand this association. It is easy to overlook more subtle signs of intellectual deficits in patients with less marked degrees of cerebral palsy. Perhaps of even greater importance is the observation that in about two-thirds of the cases of the so-called behaviour problems without well defined causes, disturbances in the brain wave pattern are to be noted. While paranatal anoxia is by no means the sole, or perhaps not even the most common, cause of these mental variations, there can be little doubt but that a large number of them do have their genesis in this situation.

The high incidence of paranatal anoxia is perhaps the most striking evidence

of its importance in the causation of *cerebral palsy*. Actual percentages vary from one series to another. As the result of study of the group of 160 cases of verified brain lesions in cerebral palsied children, the present writer concluded that about two-thirds were incident to some circulatory disturbance before or during the birth process, with anoxia as the chief pathogenetic factor. Fuldner[13] studied the possible etiological factors in 106 clinical cases of cerebral palsy and found a history of asphyxia at birth in about 90 per cent. Even if one accepts the lower of these two estimates, it is evident that paranatal anoxia is by far the most common factor in the causation of this clinical state, more than all other causes combined. This conclusion would indicate that if any material lowering of the incidence of cerebral palsy is to be expected a more critical analysis of paranatal anoxia must be made by both obstetricians and anaesthetists. This particular field of anaesthesia offers an excellent opportunity for further investigation of the possible factors involved.

Residual Paranatal Brain Lesions from Fatal Cases Occurring in Later Life

It is evident that our understanding of the pathogenesis and nature of the cerebral lesions found at autopsy in cerebral palsied individuals has been greatly delayed because of an incomplete knowledge of what can happen to the brain as a result of the anoxic states occurring in later life. This is not too surprising when it is realized that the disclosure of the ultimate lesions upon which an analysis must be made is delayed for months or years. By this time any interest in the causative factors may have been entirely dissipated. Moreover, in a community hospital, very few if any such lesions will be encountered in a lifetime. It is perhaps on this precise point that the present writer has been so fortunate, for he has had the opportunity to investigate the unusual lesions of the brain in a series of well over 65,000 autopsies in a large general hospital as well as an additional number (2,800) of coroner's autopsies. The collection of such cases that show the ultimate effects of anoxaemic states in general has been to him not only an opportunity but an obligation to the larger field of clinical medicine. This brief section, then, may be considered as a crystallization of the essential points characterizing the ultimate residual lesions of the anoxic state. Brief reference will also be made to the results of anoxia on experimental animals which fill in some important gaps in our knowledge. The experimental studies may be appropriately cited first.

The ultimate effects on the brain of experimental neonatal anoxia have been carefully investigated by Windle, Becker, and Weil.[14] By an ingenious method of impairment of the uterine blood supply of pregnant guinea pigs just prior to birth of their young, a state simulating paranatal anoxia could be produced. By following a group of these animals for a number of months, some of the ultimate effects of anoxia on the brain were demonstrated. It was observed that atrophy of the entire brain was one of the consequences of this procedure, as would ordinarily be expected. What was not anticipated, however, was that atrophy could also involve only a hemisphere or even a single lobe of the brain.

Their work therefore demonstrates that comparable situations of lobar or hemispheral atrophy as well as total atrophy of the brain could occur as a result of neonatal anoxia. This potential of the anoxic state in the newborn is important, for it is just this group of residual lesions which have been particularly difficult to evaluate in man.

In the writer's series of cases, there were several examples in which lobar and hemispheral atrophy, as well as total atrophy of the brain, had taken place. This change seemed to be the only demonstrable alteration responsible for cerebral palsy and reduced mental acuity.

What has been learned from a study of so many examples of cerebral anoxia of later life that has proven to be of help in the evaluation of the cerebral lesions dating back to birth? In the first place, it becomes clear that certain fundamental alterations, obviously due to anoxia and ischaemia, are observed in the brains of older individuals and these seem to have their counterpart in brain damaged children.[15] This group of lesions constitutes a series of alterations progressing in their simplest form from a mild degree of atrophy of a given group of cerebral convolutions to a widespread nodular cortical change. Next to this lesion, there occurs a more severe degree of cortical atrophy such as is seen in the residuals of occlusive vascular lesions which may result in actual porencephalic defects in the brain.

In the second place, the characteristic cortical change histologically constitutes a second and parallel series, existing in its mildest form in a patchy or laminar loss of nerve cells and progressing with increasing degrees of damage to the intermediate cellular lamina until either a laminar vascular scar (in less severe degree of damage) or a grossly evident laminar cortical necrosis results.

A third observation, one which parallels the cortical alterations, but which does not follow a typical pattern, is a progressive degeneration or actual softening of the lenticular nucleus. The index lesion in this respect is the softening of globus pallidus such as occurs in consequence to a severe exposure to carbon monoxide or other asphyxiant gases.[16]

The fourth observation, one that seems not to have attracted the attention which it deserves, is the tendency for certain types of anoxic disorders to result in regressive changes in the underlying white matter. Following the more severe degrees of anoxia, there results the quite rapid formation of cysts in the cerebral centrum. In a slower evolution of this process, demyelination with gliosis constitutes the ultimate lesion. These lesions can develop only under certain circumstances in which prolonged survival after an anoxic insult is the chief etiological factor. It is observed most often after carbon monoxide and nitrous oxide, and less so after exposure to other asphyxiant gases.

The fifth observation involves the cerebellum more or less diffusely, resulting in a generalized atrophy of this organ, although a few examples of focal atrophy have also been seen. This is not so commonly found after anoxias of adult life, although its basic histological lesion, a diffuse loss of the Purkinje and granule cells, occurs in a wide variety of conditions associated with a circulatory disturbance if not an obvious anoxic state. This particular feature is now under

study in the Cajal Laboratory, and a full report will be forthcoming within the next year or so.

The next observation, one within the fairly characteristic pattern of cerebral responses to lowered oxygen tension, indicates that a considerable variety of lesions may result in a single case, depending upon the mechanism and degree of oxygen deprivation. It is also possible that these changes are owing in part to the length of time the impairment of oxygen supply persists. This fact can be seen by reviewing the possible lesions in the brain which may occur after carbon monoxide "poisoning," one type of anoxia with which most of us are familiar. As the writer has pointed out in an earlier study,[17] it is possible to find (i) diffuse cortical changes with spotty and laminar necrosis, so characteristic of anoxia incident to nitrous oxide, (ii) focal haemorrhage, softening and/or formation in the lenticular nucleus (especially the globus pallidus) which, of course, is the type-lesion of carbon monoxide "poisoning," (iii) selective damage to the Purkinje and granule cells of the cerebellar cortex, (iv) the formation of gross cortical-subcortical softenings, particularly in the parieto-occipital region, (v) the formation of local cortical-subcortical cysts with longer periods of survival, (vi) multiple cyst formation in the cerebral white matter, and finally, (vii) a diffuse demyelination of the cerebral centrum. The important conclusion from this fact is that anoxia *per se* can result in a wide variety of lesions, some which may not be appreciated at all as a residual of this state.

Our seventh observation is a corollary to this fundamental fact, namely that more than one of these lesions may be present in any one case producing thereby a *lesion-complex*. Such a situation can be interpreted properly only by recognizing the individual types of cerebral changes and appreciating that all of them must have an impaired oxygen supply as their genesis. It is also possible that such a complex may result from a combination of the various forms of anoxia (anoxic, anaemic, and histotoxic forms).

Anoxia Incident to the Birth Process as a Possible Cause of Brain Damage in Infancy

The misunderstanding of the complex nature of the brain lesions found in crippled children has been due to a failure to see in these well-defined patterns of tissue change the classical hallmarks of anoxia. The first impression of the average investigator is that such lesions must be the result of some unusually complex pathogenetic process and, by inference, must be of congenital, degenerative, or infectious etiology. By applying such etiological labels to this kind of lesion, we excuse ourselves from the necessity of looking further into their causation. But to put the proposed thesis of their anoxic etiology to the test, these various lesion-complexes must be broken down and each of the lesions composing them must be examined with critical scrutiny. It will be logical to start from the more simple lesions and proceed to those which are more complex.

(*a*) *Widespread cerebral softening in infancy.* This group of lesions is relatively rare, even though the several subvarieties are grouped together. They are

usually exposed at autopsy in infants who have presented a progressive downhill course to death from within the first few months to a year or two of life. The clinical course is characterized by the early onset of convulsive seizures, followed by evidence of defective mentation, and finally by the development of quadriplegias and decorticate rigidities. The less severe lesions consist of a diffuse softening of the cerebral gray matter (Alper's disease). At times, these lesions of the gray matter are associated with subcortical or central cyst formation. In more severe cases, the softening involves both the cortex and subcortex.[18] The very localization of the physical alterations in the brain suggests an anoxic etiology. In addition, the author's recent investigation of the problem suggests that their genesis lies in some circulatory disorder occurring at the time of birth.*[19]

(*b*) *General cerebral atrophies.* The chronic counterpart of this group of lesions may be included under this term of general cerebral atrophies. This term implies that either the cerebrum as a whole, or one hemisphere, is diffusely atrophic. The convolutions individually seem to be fairly uniform in diameter but are simply smaller than normal in size. In the cases of the hemiatrophies, sections from comparative areas in the cerebral hemispheres indicate that the smaller hemisphere is marked by a patchy loss of cortical nerve cells. Even in these presumed hemiatrophies, the larger hemisphere is smaller than that in the average child of corresponding age. This is suggested even during life, for the head of the affected child is inclined to be smaller than average. Roentgenograms of the skull often show a smaller cranial vault on the side of the smaller hemisphere. As a basis for consideration of etiology, the experimental work of Windle and his associates[14] gives us the clue in an anoxic episode either just before or at the time of birth. This factor may be of the nature of a lessened circulatory irrigation, although a straight anoxic episode at the time of birth may have taken place. As Windle *et al.* have demonstrated, it was not unusual to find in their animals what appeared to be a generalized anoxic process, could cause an atrophy of one hemisphere or even a solitary lobe of the brain.

(*c*) *Focal cortical scars or cysts.* Ford[6] and Penfield and Erickson[7] have pointed out that focal cortical scars or cysts may be the cause of epileptiform convulsions, often characterized by localizing phenomena. When these small lesions are examined microscopically, they prove to have the identical structure of nodular cortical atrophy (or sclerosis), with their characteristic anoxic changes in the cerebral gray matter. These findings suggest that such lesions have their genesis in a mild form of paranatal anoxia, but one in which the secondary and perhaps more obvious ischaemic changes have produced the essential epileptogenic lesions. This aspect of the problem will be considered in greater detail in a subsequent section.

(*d*) *Cerebellar atrophies.* A great deal of work has been done on atrophy of the cerebellum in the recent past. This work certainly proves that a reduction

*Rarely these widespread cortical lesions undergo a slower process of deterioration with a generalized loss of the parenchymatous elements and with a replacement gliosis; under these circumstances a cortical change designated as a "walnut kernel" brain results

in size of the individual cerebellar folia in many, if not most, cases cannot be laid at the door of cerebral anoxia. But in some cases, cerebral anoxia is indeed the actual cause. This has already been suggested clinically by the group of the so-called cerebral palsied children whose predominant symptom-complex is that of ataxia-atonia. This is also implied by the disclosure by specific examination of the cerebellar tissues in cases whose other lesions are characteristically of anoxic etiology.[19] It would therefore appear that these structural alterations in the cerebellum are present in minor degrees in many instances of cerebral palsy, but in these the suggestive cerebellar manifestations are obscured by the predominant cortical or ganglionic symptoms. Much more study of the accompanying cerebellar changes is necessary to evaluate more completely the unequivocal examples of the ataxic-atonic group.

(*e*) *The nodular atrophies* (*or scleroses*). The most common basic lesion of the brain in cerebral palsied children is this irregular atrophic and sclerotic change in portions of the cerebral cortex. In fact, a variety of distributions of this change may be found in any large series of cases.[20] Such examples can be compared in all their detail to ischaemic lesions of the cortex in older individuals with arteriosclerosis.[21] This seems to establish without question the pathogenesis of the lesion. But it is also necessary to recognize from other experiences with the anoxic state that oxygen lack may set in motion a degree of vasomotor dysfunction which produces this secondary or ischaemic type of lesion. This may occur either in the form of the epileptic lesions of Ford[6] and Penfield and Erickson,[7] the so-called lobar sclerosis of Bresler,[22] or finally as the diffuse lesions seen in severe cases of nodular sclerosis.[20] This lesion is commonly associated with porencephalic cysts (which are but an advanced degree of the same process), alterations in the basal ganglia, or even cystic formations in the central white matter. These combinations further demonstrate the truth of one of the postulates already set forth to the effect that multiple lesions, all of anoxic etiology, may be found in a single case.

(*f*) *The ganglionic-cortical lesions.* Still another group of lesion-complexes are those which involve the basal ganglia and, to a lesser extent, the cerebral cortex. The predominant lesion affects various ganglionic structures or subganglionic nuclei so that the outstanding clinical symptom is that of various hyperkinetic states, most commonly that of choreoathetosis. This group of cerebral palsied children are recognized as a separate clinical entity on this basis. The most common lesion seems to be that of status marmoratus, a peculiar change characterized by the presence of an increased number of bundles of myelinated nerve fibers, occurring chiefly within or near the ganglionic masses but involving the cerebral cortex at times. Status dysmyelinisatus (degeneration of the myelinated nerve fibers) is much more rare. Cysts or atrophy affecting the lenticular nucleus are also described. Although the pathogenesis of status marmoratus is still a subject of much conjecture, but possibly due to secondary destruction of cortex in embryonic life,[23] most students of the problem agree that this lesion is a consequence of "birth injury".[24] Because this lesion is so often associated with other changes in the brain characteristic of cerebral anoxia, it seems logical to assume that it also is of an anoxic etiology.

(g) *Lesions of the central white matter.* The structural alterations in this group of lesions involving the cerebral white matter have divided the investigators studying these lesions into several camps. As for *gliosis*, the least important of the three, there is perhaps little to say other than its association with so many other lesions of the group here considered speaks strongly in favour of its origin in some diffuse circulatory process such as anoxia. The second lesion described as *chronic infantile cystic degeneration of the cerebral white matter* is believed by a larger portion of investigators to be the result of multiple haemorrhages incident to occlusion of the internal venous system of Galen. The present writer cannot accept this thesis for reasons brought out in a recent publication.[25] Moreover, he has had the opportunity to study a series of three recently born infants whose fatal lesion appeared to consist of a widespread condensation of multiple petechial haemorrhages occupying most of the cerebral white matter.[25] Since multiple haemorrhages into the cerebral centrum are characteristic of acute anoxia under other circumstances, and since in the cases studied there was evidence of an anoxic episode at birth, it seems reasonable to believe that neonatal anoxia may well have been its cause.

As for the third possibility, *diffuse demyelination of the cerebral white matter*, otherwise described as the infantile form of diffuse sclerosis (Schilder's disease), there is still room for uncertainty. Perhaps the greatest reason for doubt lies in the fact that in many cases there is a familial history of this disorder. There is a form which occurs in later childhood and another which develops in later life (Pelazeus-Merzbacher's disease)—still another argument against its genesis in a paranatal anoxic episode. Nevertheless, the fact remains that every detail of the histology of diffuse sclerosis has its exact counterpart in widespread degeneration of the cerebral white matter after serious exposure to carbon monoxide. Therefore, this etiology demands consideration for this possible cause, be it paranatal or otherwise. We are obliged to leave this problem at this point.

A survey of these lesion-complexes associated with, and presumably the cause of, cerebral palsy beginning in early life suggests that in from two-thirds to three-fourths of these patients a paranatal anoxic episode is their most common cause. This conclusion is based on the fact that when these complexes are analysed in the light of the cerebral changes incident to oxygen want of later life, their similarities argue in favour of an anoxic episode. Other changes (the general atrophies) resemble post-anoxic alterations in experimental animals. In still other lesions (status marmoratus) whose pathogenesis is difficult to evaluate, there is a clinical history of "birth injury" in the great majority of instances. As has already been pointed out, the presence of multiple lesions, each of which has been shown to have a possible anoxic etiology, constitutes still another argument in support of this conclusion.

Relation of the Anaesthetist to Birth Palsies

It would be idle to discuss at length the problems of paranatal anoxia without condensing this material into some practical conclusions, for, while many anaesthetists may have an academic interest in the problem of cerebral palsy

because of the connection between anoxia at birth and its clinical consequences, any direct concern must lie in the more practical problems of the administration of anaesthesia to the mother-to-be at the time of delivery. What part, if any, is played by the anaesthetist in the production of anoxic damage to the brain of the newborn child? To the credit of the profession, the answer is "very little, if any." Nevertheless, it is well to review very briefly what the possibilities may be.

In the recent past, there has been an increasing demand on the part of women to be completely emancipated from the pain, if not the consciousness, of childbirth. It would appear as though the would-be-mothers were anxious, not only to be completely free of any discomfort in the process, but also to be completely oblivious to the entire proceedings. In view of this insistence, the obstetrician tends to put pressure on the anaesthetist to give the anaesthetic early, and to maintain it until the procedure is completed. But meanwhile, the evidence has accumulated that the more sedation and anaesthesia that has been administered, the more likely it will be that the infant will be born in a state of apnoea. Moreover, the length of this period of apnoea is proportional to the degree of narcosis produced.[11] It must be recognized that apnoea *per se* is probably not significant in the great majority of cases. But there are, nevertheless, two inherent dangers. The first danger lies in the possibility that, together with the increased depth of narcosis, the intercurrence of some other factor, such as a prolonged or difficult delivery or excessive haemorrhage, may superimpose two situations which add up to a serious degree of anoxia. The second danger lies in the fact that often this additional factor may be totally quiescent clinically so that the birth is presumed to be normal when it is not. This is evident in that in so many cases of cerebral palsy in which the cerebral lesion is unequivocally due to anoxia, there is nothing in the birth record to point to the exact causative factor. If the writer's long experience in the problem of paranatal anoxia has any meaning whatever, the most important contribution which he can make to the profession of Anaesthesia is this spectre of "silent anoxia," or hypoxia, if you please, which must reduce the mentality and cripple the limbs of so many of our children. How low the degree of narcosis that one can produce and still accomplish the legitimate purpose of anaesthesia, not how much anaesthesia can be produced and still be able to revive the infant, should be the studied objective. It is not any fear of what may happen to the mother, but a fear of what may happen to the brain of the newborn infant, whose very vulnerable nervous tissues are much more susceptible to the effects of oxygen want, that should be the guiding principle of practice of the art of anaesthesia under these circumstances.

REFERENCES

1. WIGGERS, C. J. Cardiac Adaptions in Acute Progressive Anoxia. Ann. Int. Med. *14* (1): 1237-1247 (1941).
2. LITTLE, W. J. On the Nature and Treatment of the Deformities of the Human Frame. London: Longman, Brown, Green, and Longman (1853).

3. OSLER, W. The Cerebral Palsies of Childhood, a Clinical Study from the Infirmary for Nervous Diseases. Philadelphia: P. Blaskiston (1889).
4. FREUD, S. Die infantile Cerebrallähmung. Wien: Alfred Holder (1897).
5. BEECHER, H. K., & TODD, D. P. A Study of Deaths Associated with Anesthesia and Surgery Based on a Study of 599,548 Anesthesias in Ten Institutions, 1948-1952, Inclusive. Ann. Surg. *140* (1): 2-35 (1954).
6. FORD, F. R. Cerebral Birth Injuries and their Results. Medicine *5* (5): 121-194 (1926).
7. PENFIELD, W., & ERICKSON, T. Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment, and Prevention of Epileptic Seizures. Springfield, Ill.: Charles C. Thomas (1941).
8. NIELSEN, J. M. Etiology of Idiopathic Epilepsy. Bull. Los Angeles Neurol. Soc. *11* (3): 97-101 (1946).
9. NIELSEN, J. M., & BUTLER, F. O. Birth Primacy and Idiopathic Epilepsy. Bull. Los Angeles Neurol. Soc. *13* (3): 176-178 (1948).
10. NIELSEN, J. M., & COURVILLE, CYRIL B. Role of Birth Injury and Asphyxia in Idiopathic Epilepsy. Neurology *1* (1): 48-52 (1951).
11. COURVILLE, CYRIL B. Narcosis and the Fetal brain. Bull. Los Angeles Neurol. Soc. *20* (3): 97-111 (1955).
12. BENDA, C. E. Developmental Disorders of Mentation and Cerebral Palsies. New York: Grune & Stratton (1952).
13. FULDNER, R. V. Labor Complications and Cerebral Palsy. Am. J. Obstet. & Gynec. *74* (1): 159-166 (1957).
14. WINDLE, W. F., BECKER, R. F., & WEIL, A. Alterations in Brain Structure after Asphyxiation at Birth: An Experimental Study in the Guinea Pig. J. Neuropath. & Exper. Neurol. *3* (4): 224-238 (1944).
15. COURVILLE, CYRIL B. Antenatal and Paranatal Circulatory Disorders as a Cause of Cerebral Damage in Early Life. J. Neuropath. & Exper. Neurol. *18* (1): 115-139 (1959).
16. COURVILLE, CYRIL B., & MYERS, R. O. Effects of Extraneous Poisons on the Nervous System. III. The Asphyxiant Gases. Bull. Los Angeles Neurol. Soc. *19* (4): 197-225 (1954).
17. COURVILLE, CYRIL B. Case Studies in Cerebral Anoxia. IX. The Cerebral Lesion-Complexes Incident to Carbon Monoxide Asphyxia. Bull. Los Angeles Neurol. Soc. *20* (3): 139-144 (1955).
18. COURVILLE, CYRIL B. Syndrome of Decorticate Rigidity, Convulsions, and Amentia Occurring in Early Infancy: Review of the Literature and Report of Four Verified Cases with Subtotal Softening of the Forebrain. Bull. Los Angeles Neurol. Soc. *25* (1): 1-17 (1960).
19. COURVILLE, CYRIL B. Structural Alterations in the Cerebellum in Cases of Cerebellar Palsy: Their Relation to Residual Symptomatology in the Ataxic-Atonic Group. Bull. Los Angeles Neurol. Soc. *24* (3): 148-165 (1959).
20. COURVILLE, CYRIL B. Pathogenesis of Nodular Atrophy of the Cerebral Cortex: A Common Cortical Change Found in Cases of Cerebral Palsy. Arch. Pediat. *77* (3): 101-129 (1960).
21. COURVILLE, CYRIL B. The Pathogenesis of Nodular Cortical Atrophy: Apparent Mechanism of Lesion Commonly Found in Cerebral Palsied Individuals. Bull. Los Angeles Neurol. Soc. *22* (3): 120-130 (1957).
22. BRESLER, J. Klinische und pathologisch-anatomische Beiträge zur Microgyrie. Arch. Psychiat. *31* (1): 566-573 (1898-1899).
23. MORRISON, L. R. Anatomical Studies of Central Nervous System of Dogs without Forebrain or Cerebellum. Haarlem: Bonin (1928). Cited by Benda (1952).
24. MALAMUD, N. Status marmoratus: A Form of Cerebral Palsy Following either Birth Injury or Inflammation of the Central Nervous System. J. Pediat. *37* (10): 610-619 (1950).
25. COURVILLE, CYRIL B. Residual Lesions after Thrombosis of the Superior Longitudinal Sinus: Review of Literature and Report of Case. Bull. Los Angeles Neurol. Soc. *23* (4): 160-170 (1958).
26. COURVILLE, CYRIL B. Central Hemorrhagic Encephalopathy of Early Infancy: Report of Three Verified Cases Suggesting the Genesis of Infantile Cystic Degeneration in a Paranatal Anoxic Disorder. Neurology *10* (1): 70-80 (1960).

ELECTROGRAPHIC REFLECTIONS OF CEREBRAL HYPOXIA*

WILLIAM C. GIBSON, M.D., PH.D.†

ANAESTHETISTS ARE one of the few groups of strictly human physiologists left in the world of science today. The World War II emphasis on the investigation of pressing human problems by addressing oneself to human subjects, instead of toads, frogs, clams, and cats, has been lost, unfortunately. It is to anaesthetists and to human cardiopulmonary laboratories that we look today for a continuance of that most vital of all disciplines in medicine, "Clinical Science," as pioneered by Sir Thomas Lewis.

This is particularly true with reference to electroencephalography, where the very complexity and phylogenetic development of the human brain makes generalization from cat and dog observations not merely hazardous, but often meaningless. This presentation will discuss some clinical investigation carried out during the past year in association with Professor Henri Gastaut and his colleagues at the Laboratory of Neurobiology at Marseille. The detailed reports of this work are published elsewhere.[1,2,3,4] This review will dwell on the principles involved in the investigations and on findings having particular application in the field of anaesthesia.

We have been concerned with neuronal changes, studied electrographically, in the cortex and subcortex of the human brain as hypoxia becomes complete anoxia. The work has proceeded in the following sequence: (1) A study of cerebral anemia following reflex cardiac slowing or temporary arrest, induced by ocular compression; (2) EEG changes following Valsalva's manoeuvre; (3) Hemispheral and bilateral cerebral anaemia induced by carotid sinus and artery compression; (4) Cerebral hypoxia from hyperventilation, or anoxia from the breathing of pure nitrogen.

(1) Forceful, sustained digital compression of both eyeballs simultaneously has been a parlour trick and laboratory diversion for many generations. It is likely to become, however, in an age of electrical recording from the brain, a most useful tool in differentiating syncopal cases from epileptics. The work at Marseille in this field was financed by the United States Air Force in an attempt to find simple methods of clinical investigation applicable to aircrew candidates in their second decade of life.

As can be seen from Figure 1, 10 sec. of forceful bilateral ocular compression have arrested the heart for approximately 12 sec., as shown by the electrocardiographic tracing (channel 7). Respiration is unaffected in this, as in most, cases. However, the arrested heart fails to pump freshly oxygenated blood to the brain, with the result that the EEG shows bilaterally abnormal electrical

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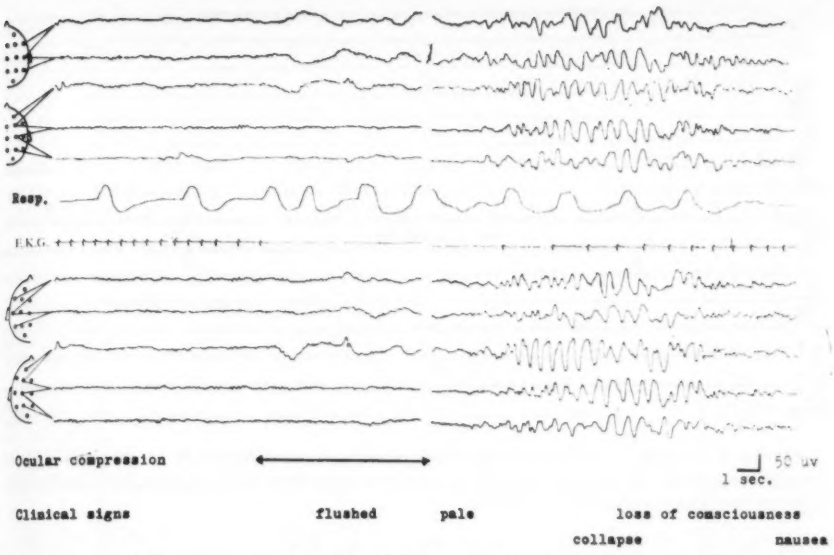

FIGURE 1. Ocular compression for 10 sec. (black bar) producing cardiac arrest (12 sec. approx.) with resultant slow waves bilaterally in EEG, and associated loss of consciousness.

activity. Another 10 sec. elapse before the re-established heart contractions can return the EEG to normal. During this period, collapse and loss of consciousness are seen to supervene briefly. Usually the blood pressure becomes so low as to be unmeasurable by the ordinary manometric method. A very high correlation was found between a positive oculocardiac reflex effect and a history of fainting in childhood or adolescence.[2] The lower the age group the higher was the incidence of reflexly induced cardiac arrest. Patients over the age of 45 years were not nearly as susceptible to this test, but, as we shall see later, they are increasingly susceptible to carotid sinus compression.

Anaesthetists are only too well aware of the extreme danger of cardiac arrest during ophthalmological operations, such as the correction of strabismus, in very young children. Kirsch *et al.*[5] have shown the facility with which traction on the internal rectus muscle will stop the heart. My attention was recently drawn to an unfortunate case of a young boy whose eye had been penetrated by a barbed arrow. Only after much difficulty and manipulation was the arrow removed, by which time the child had suffered a prolonged cardiac arrest. As a result, cerebration is almost lacking in this patient today.

The trigeminovagal reflex arrest of cardiac function is but one of a dozen examples which might be cited in a study of cerebral ischaemia of reflex origin. There are many vagovasal reflex patterns directly applicable to the anaesthetist's problems of bowel surgery (gall bladder interventions particularly), chest and tracheal manipulations. A discussion of preventive measures will follow the presentation of our data.

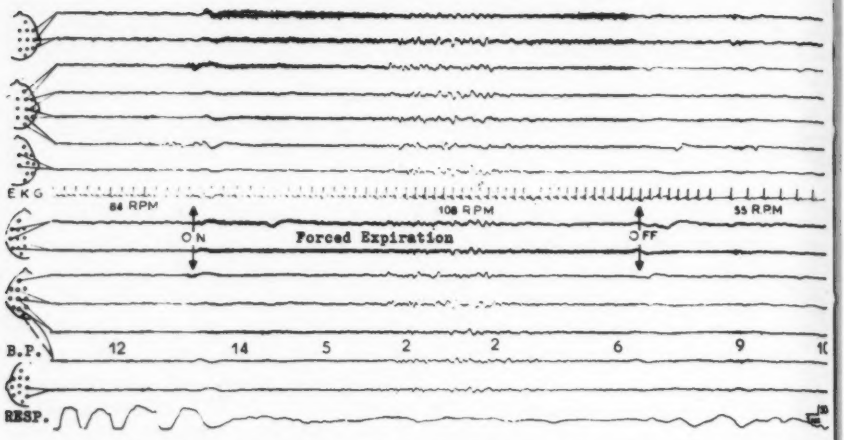

FIGURE 2. Forced expiration during which slowing is seen bilaterally in the EEG. Blood pressure drops from 120 mm. Hg, systolic, to an approximate level of 20 mm. Hg. Note acceleration of heart rate and cessation of respiration.

(2) Valsalva's forced expiration, such as that used in the 40 mm. Hg test during aircrew examinations in two wars, may have some remarkable effects on cerebral circulation. Figure 2 shows the bilateral slowing seen in the EEG in a patient being investigated for ptussive syncope. The lowest line of this figure shows the suspension of respiration, and the drop in blood pressure from 120 mm. Hg to a much lower figure, with an eventual rise to 60 mm. Hg as the expiration is terminated. The heart rate increased to 108 per min. While the causal mechanism is not generally agreed upon, the cerebral hypoxia, as shown in the EEG, is undoubted in these cases.

(3) Over the age of 45 years, cerebral ischaemia from carotid or vertebral arteriosclerosis is a problem of great significance to anaesthetists. Figure 3

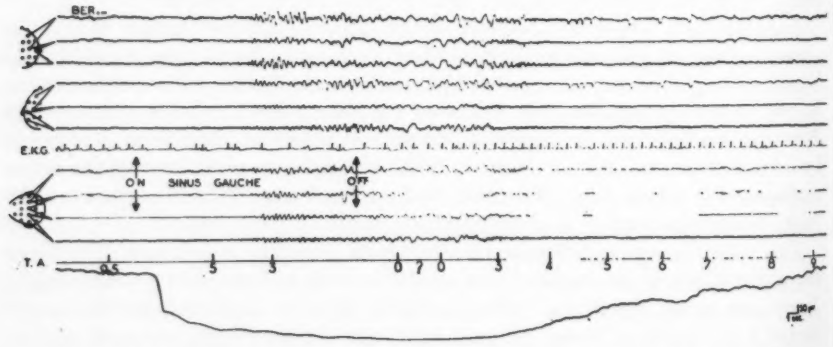

FIGURE 3. Effect of forceful pressure on left carotid sinus for 10 sec. with limited effect on heart rate but with marked effect on systolic blood pressure, and on EEG.

demonstrates slowing of cerebral electrical rhythms secondary to vascular collapse when the area of the carotid sinus is forcefully compressed. The effect on the heart rate is minimal, but on the blood pressure it is very serious. With re-establishment of the previous blood pressure all EEG abnormality is erased. Possibly because of changes in the adjacent tissue of the vessel wall, the carotid sinus itself becomes more sensitive with increasing age. However, sinus stimulation must be taken in conjunction with common carotid compression, if not temporary obstruction, in the tests here described. The EEG is one of the most sensitive and most easily recorded indicators of the function of (*a*) the carotid arteries, and (*b*) the collateral circulation available, through the Circle of Willis, from the opposite hemisphere.

(4) Forceful hyperventilation has for many years been a standard technique employed to "activate" the EEG. As Figure 4 shows, the blowing off of CO_2

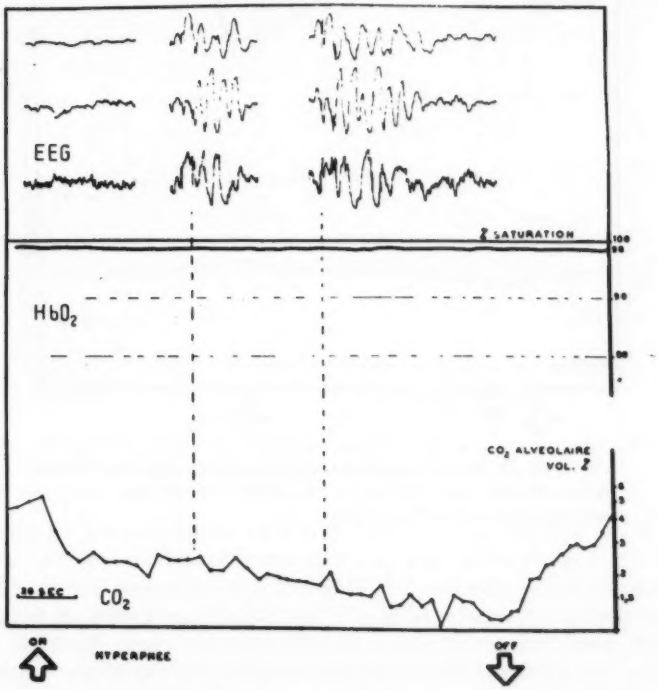

FIGURE 4. A marked loss of carbon dioxide, through hyperventilation, fails to affect the oxyhaemoglobin saturation, but leads to marked EEG changes.

leads to no decrease in oxyhaemoglobin saturation but to a marked change in the EEG. The appearance of the slowest cortical waves coincides with the lowest level of alveolar CO_2. As Figure 5 suggests, the inhalation of pure nitrogen ("a-zote" in French, meaning the gas which will not support life)

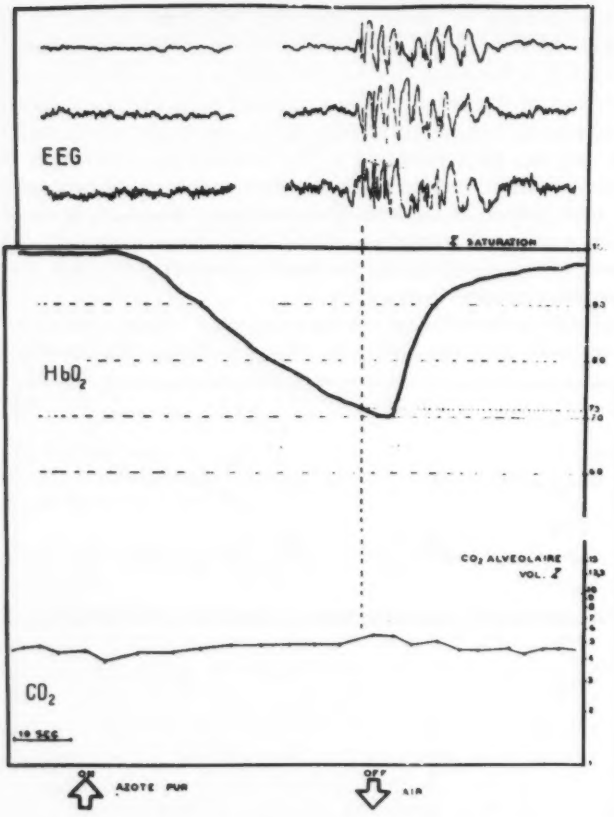

FIGURE 5. Pure nitrogen breathing fails to affect the alveolar carbon dioxide, but produces marked EEG effects when the oxyhaemoglobin reaches 70 per cent.

has no effect on the alveolar CO_2, but it has an effect on the EEG identical with that during hyperventilation (Fig. 4). This hypoxic effect is evident when the oxyhaemoglobin saturation approaches 70 per cent. We thus feel that hyperpnea and pure nitrogen inhalation produce their common hypoxic effect on the EEG by cortical capillary constriction and by hypoxaemia, respectively.

When, as shown in Figure 6, carbon dioxide is added to the nitrogen to be inhaled, it is found necessary to drive the oxyhaemoglobin down to a figure of 50 per cent in order to evoke marked slow wave activity in the cortical EEG.

In practice, the pure nitrogen was inhaled through an open circuit for an average of 40-50 sec., by which time hypersynchronous slow waves would usually appear in the EEG, as indicated in Figure 7. The onset, in the case of the petit mal epileptic there illustrated, was, as in most cases, very sudden

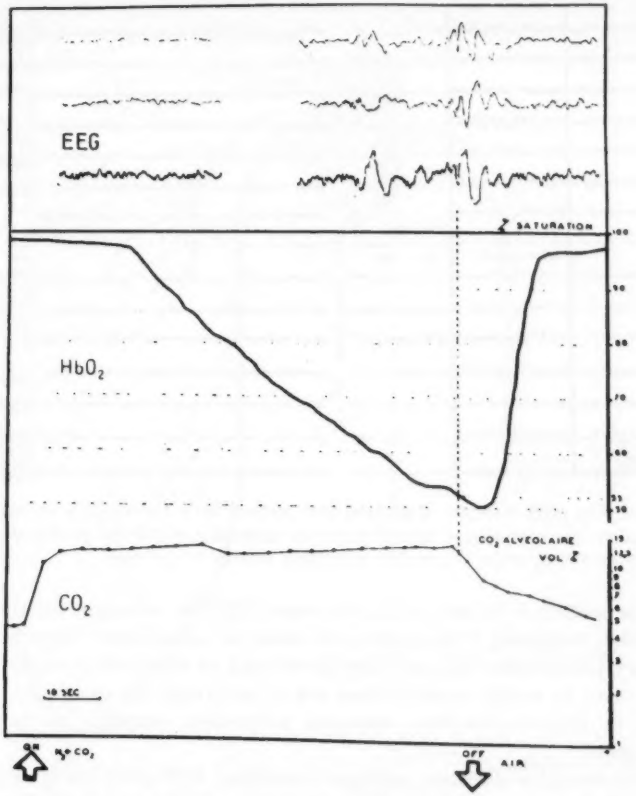

FIGURE 6. A mixture of carbon dioxide and nitrogen produces EEG effects only as the oxyhaemoglobin approaches 50 to 55 per cent.

and dramatic. An immediate switching over to pure oxygen, or 95 per cent oxygen-5 per cent carbon dioxide mixture was always practised. In many hundreds of tests, carried out with these precautions, no accidents occurred.

It should be mentioned that in children it was found useful to add a small amount of oxygen to the nitrogen inhaled to slow down the appearance of slow activity in the EEG in order that it could be studied adequately.

Nitrogen inhalation activated the EEG record in approximately 60 per cent of the generalized epileptics. The remaining 40 per cent were shown up electrographically by photic stimulation. The former group in no way overlapped the latter. Nitrogen proved to be better at activating generalized epileptic cases than hyperventilation.

In cases of focal epilepsy, nitrogen breathing promoted the appearance of localized discharges where none were seen in the resting record. It also had the effect of reinforcing any existing EEG focal abnormalities. While not quite as

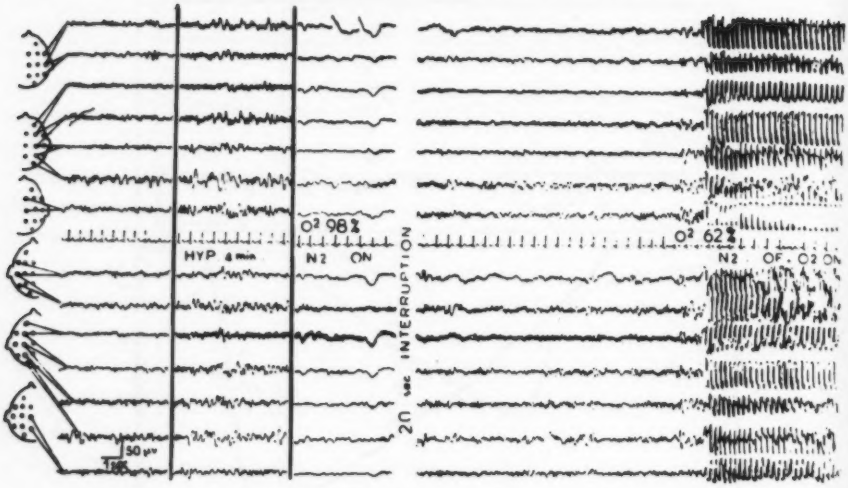

FIGURE 7. The petit mal case illustrated here showed little abnormality at rest or during hyperventilation. The breathing of pure nitrogen for approximately 50 sec. produced a spike and wave pattern bilaterally when the oxygen saturation reached 62 per cent.

effective as metrazol in activating abnormal EEG's, nitrogen inhalation was nevertheless considered to be safer and easier to administer. Nitrogen caused no olfactory phenomena such as those attributed to metrazol by some workers. In senile cases in which explanations are of no avail, for example, as to the technique of hyperventilation, nitrogen inhalation presents no problem in administration.

In cerebrovascular diseases, nitrogen breathing will often bring out quickly a focal EEG change or increase the voltage in a particular area of the cortex. If the patient is then switched on to pure oxygen such cases show an immediate replacement of the nitrogen-induced abnormality, and even of the pre-existing abnormality.

DISCUSSION

Cerebral hypoxia presents an anaesthetic problem second to none, whether it be due to true anoxia or to cerebral ischaemia. The latter is so intimately related to cardiac arrest that the anaesthetist of today must be a human physiologist alert to cardiac as well as to respiratory problems. Nor is the role of the anaesthetist to be a passive one in this field; otherwise the patient's brain may suffer, and the anaesthetist will be blamed for the subsequent poor recovery.

Preventive measures lie in the anaesthetist's province and he would be wise to use them unreservedly. If the choice lies between giving 1/50 of gr. of atropine intravenously just before an operation, or ripping a chest open after cardiac arrest has occurred, the former would seem preferable. Atropine will protect

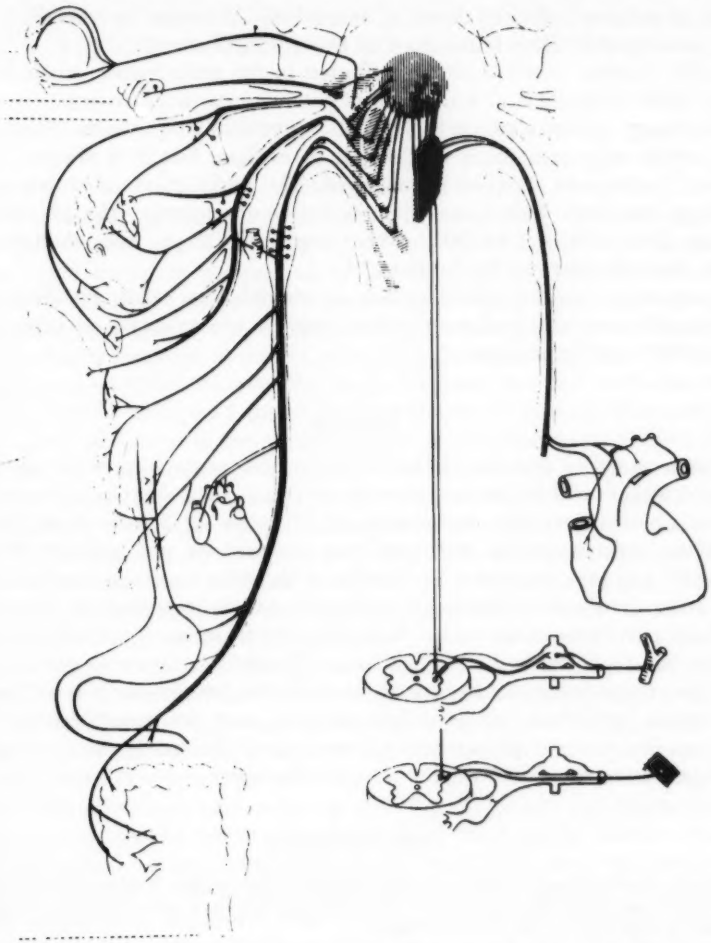

FIGURE 8. Reflex pathways (sensory on left, motor to heart on right) involved in cardiac arrest.

the heart from the acetylcholine released by the vagus nerve endings, and it is here that the final step in the reflex arc can be interrupted (Fig. 8). True, good anaesthesia will reduce the likelihood of reflex arcs being completed, but it is important to realize that in the case of the trigeminal nerve, to take but one example, one can still slow or stop the heart by ocular compression.

The elementary fact which is too often overlooked is that atropine protects the heart in successful or unsuccessful anaesthesia. Cardiac arrest during intubation, during a bronchogram, or during gall bladder manipulation with its vagovasal reflex arc is too common an occurrence to be dismissed as mere

failure to achieve sufficient depth of anaesthesia. Atropine in something more than homeopathic doses is required to prevent such arrest.

Finally, cardiac arrest is often attributed to the anaesthetist, when, in fact, it may more fairly be laid at the door of extensive extraocular, tracheal, gut or genitourinary procedures performed on apprehensive patients. Syncope of reflex origin may sometimes be difficult to explain, but it is always easy to prevent if adequate atropine is employed. The perfunctory administration of 1/150 gr. one hour before operation is really not meeting the physiological problem. It is now well established that doses of 1/10 gr., once thought to be heroic, are well tolerated by humans.[6,7]

In summary, then, cerebral anoxia is amenable to study by electroencephalographic methods and such studies suggest the necessity of interrupting vagal reflex arcs by atropine.

Résumé

Nous avons fait une description d'études électrographiques sur les modifications s'opérant dans les neurones de la région corticale et sous-corticale du cerveau humain au cours du passage de l'hypoxie à l'anoxie complète. Les conditions expérimentales employées ont consisté en une anémie cérébrale provoquée par la compression de l'artère et du sinus carotidiens ou à la suite d'un arrêt cardiaque temporaire provoqué par la compression des globes oculaires, par l'expiration forcée Valsalva, l'hypoxie par hyperventilation et l'anoxie par l'inhalation de 100% d'azote. Toutes ces épreuves peuvent produire des effets sérieux sur le cerveau surtout chez les personnes sensibles. Ces phénomènes soulèvent un problème sérieux pour les anesthésistes; nous suggérons des mesures préventives et, tout particulièrement, nous conseillons de couper les arcs réflexes vagaux avec de l'atropine.

REFERENCES

1. Gastaut, H.; Bostem, F.; Naquet, R.; & Fernandez-Guardiola, A. L'activation hypoxique de l'EEG par inhalation d'azote. I. Premier résultats obtenus dans les épilepsies généralisées. Rev. neurol. (Paris) *100*: 501-510 (1959).
2. Gastaut, H., & Gibson, William C. Electrographic Study of Syncopal Predisposition. Aerospace Med. *31*: 531 (1960).
3. Gastaut, H.; Bostem, F.; Fernandez-Guardiola, A.; Naquet, R.; & Gibson, William C. Hypoxic Activation of the EEG by the Inhalation of Nitrogen. II. Preliminary Report on Results Obtained in Cases of Partial Epilepsy. In press.
4. Gastaut, H., *et al.* Hypoxic Activation of the EEG by the Inhalation of Nitrogen. III. Preliminary Results Obtained in Patients Suffering from Cerebrovascular Disease. In press.
5. Kirsch, R. E., *et al.* Electrocardiographic Changes during Ocular Surgery and their Prevention by Retrobulbar Injection. A.M.A. Arch. Ophth. *58*: 348-356 (1957).
6. Ward, A. A. Atropine in the Treatment of Closed Head Injury. J. Neurosurg. *7*: 398-402 (1950).
7. McNair, F. E. Personal communication.

A LOOK AT CURRENT IDEAS ON HYPOXIA*

R. P. HARBORD, M.D., F.F.A.R.C.S.†

ONE DAY in April this year, I had an interesting experience which bears upon anoxia and its problems. I was walking down a corridor when a nurse passed by with a patient sitting propped up on a trolley inhaling oxygen from a bag and mask. I asked the nurse if she needed help, but she said she did not. I followed, almost instinctively, to the ward where the patient was lifted into bed and a staff nurse took over. She re-applied the mask with the "V"-shaped part resting against the chin. At this stage I showed her how to fit the mask accurately, but in doing so I found the bag almost stationary. The patient's face was pale except for deeply cyanosed lips; she seemed to be able to signal a response—by a slight jerky movement—but could not talk. After increasing the flow of oxygen from the cylinder I began to compress the bag intermittently (with the expiratory valve almost closed), and was able to effect inflation of the chest. The lips became less cyanosed. Artificial respiration was continued. A glance at the case notes revealed a diagnosis of bronchopneumonia. This was made by the casualty medical officer who had given nikethamide before sending her to the ward. Apparently the history was of only three days of illness.

Soon emergency resuscitative kit arrived and at this stage the patient became violent and had to be held down. Suxamethonium (50 mg). was given into a vein and a cuffed tube was passed by laryngoscopy through the glottis. The tube rapidly filled with mucus and became blocked. Suction cleared the tube and artificial respiration was then continued without difficulty. The patient appeared to be unconscious and would not respond at all. Subsequently she was handed over to the Respiratory Unit of the hospital where a tracheotomy was carried out and artificial respiration continued using relaxant drugs. After about one week the patient was able to breathe again on her own. She was discharged from hospital a week later, and although no precise diagnosis was ever made (many investigations were negative), it was thought that her illness had been due to some form of encephalitis.

From this episode several points emerge.

(1) Anaesthetists can play a useful role in the emergency treatment of anoxic patients suffering from various diseases.

(2) Resident medical officers and nursing staff of all grades should receive an intensive training from anaesthetists in the diagnosis of respiratory failure and in resuscitation. Particular emphasis should be placed upon the intermittent positive pressure method of artificial respiration using simple equipment.

(3) Respiratory resuscitation equipment, including suction, should be in every hospital ward.

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The end results of anoxia have been studied extensively by Courville[1] who has contributed much to our knowledge of this aspect of the subject. The standard concepts by Saklad[2] and by Dripps and Comroe[3] of different types of anoxia are common knowledge and serve to show how the state cannot be assessed by any single test, for example, the so-called physiological test.[4] That the oxygen saturation can be considerably reduced without the appearance of cyanosis has been established,[5] which indicates how the recognition by clinicians of this state may be difficult. A knowledge derived from pulmonary ventilation and other respiratory measurements may in future do much to help the anaesthetist avoid anoxia.

The anoxic hazard has altered with changes in anaesthetic procedure. The greater use of endotracheal anaesthesia, although it has contributed to anoxia at times, has, in general, reduced the hazard. The same may be said of the era of relaxant drugs. At first anoxia probably accounted for some of the deaths, but as anaesthetists became more accustomed to their use, so the hazard declined. The so-called circulatory deaths from relaxants[6] were in all probability primarily anoxic in origin.

The use of relaxant drugs during anaesthesia has made anaesthetists more conscious of the need to maintain an adequate pulmonary ventilation so as to interfere as little as possible with respiratory functions, either in terms of carbon dioxide elimination or of oxygen lack. As a result of this change, techniques developed in which artificial respiration replaced spontaneous respiration. This applied particularly to abdominal work. At first there was considerable opposition, for it was maintained that a functioning respiratory centre was preferable, especially as some patients developed persistent curarization post-operatively.[7] However, it seems that artificial respiration for abdominal operations has become almost a routine in some quarters. Further work by the Liverpool school under Professor Gray[8] has resulted in a technique with a sleep dose of thiopentone (sometimes the induction is with nitrous oxide and oxygen), nitrous oxide and oxygen, full curarization, and artificial respiration with *hyperventilation*.

Techniques with hyperventilation result in a low arterial tension of carbon dioxide and a high pH. This state causes a reduction of the blood flow through the brain. This may or may not result in cerebral hypoxia—a good deal will depend upon the demand for oxygen which will be reduced by anaesthesia—however, there is an additional effect which is that the high pH will shift the oxygen dissociation curve to the left so that the haemoglobin holds on to its oxygen more strongly, with the result that the tissues may suffer from oxygen lack although the blood is well oxygenated.

In contrast, the introduction of Fluothane has resulted in techniques which may influence anaesthetists in such a way as to encourage them to allow patients to breathe spontaneously during even upper abdominal operations. Fluothane is gaining in popularity because it is non-explosive and relaxes skeletal muscles. One particular advantage is that respiratory spasm is a good deal less than with the older agents such as diethyl ether. Respiratory records show when anaesthesia is too light for surgery how the respiration may increase in volume, instead of decreasing by inhibition (Fig. 1). More Fluothane may

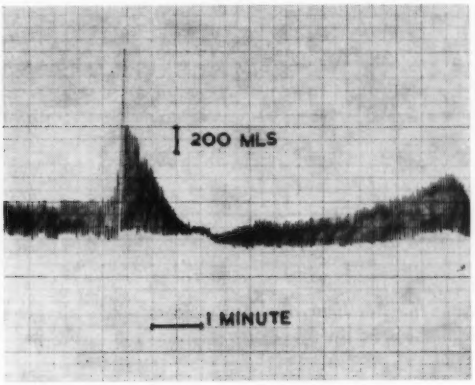

FIGURE 1. Effect of increasing the concentration of Fluothane on respiration of a patient being stimulated by surgery.

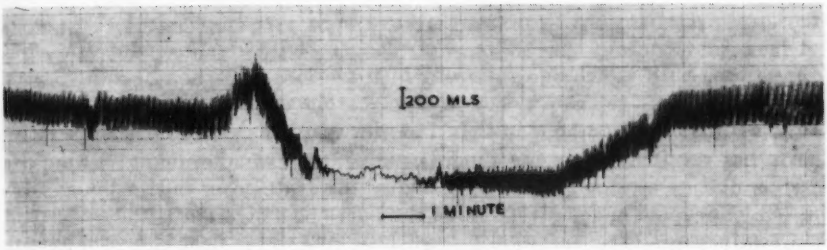

FIGURE 2. Respiratory depression to the point of apnoea with Fluothane on opening the peritoneal cavity.

be added by inhalation and the depth increased rapidly. Respiratory depression (Fig. 2) depends to some extent upon several factors, but it is possible to conduct anaesthesia with Fluothane in the closed circuit (using the technique advocated by Marrett[9]) with a minimal amount of respiratory depression, and with only short periods of more profound reduction in ventilation for opening and closing the peritoneal cavity (Fig. 3). The patient breathes a high concentration of oxygen and induction is with a sleep dose of thiopentone with atropine (to reduce the effect of Fluothane in slowing the heart). Suxamethonium is used before intubation, but thereafter no more relaxant is injected because sufficient relaxation results from the Fluothane. Nitrous oxide is not used. With this technique there is a high tension of oxygen, a high tension of carbon dioxide, and a low pH in arterial blood. The oxygen dissociation curve will be shifted to the right, and in consequence the haemoglobin's affinity for oxygen will be reduced so that its transport to the tissues is facilitated. On the other hand, the high oxygen mixture respired may reduce cerebral blood flow so as to produce a tendency towards anoxia; this, however, may not be a feature of importance.

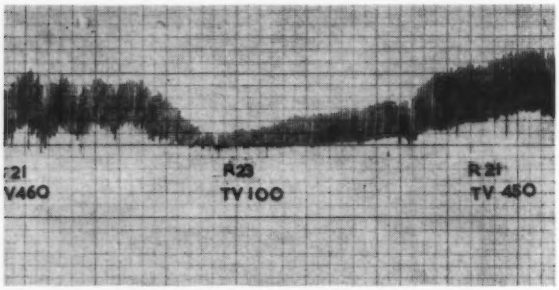

FIGURE 3. Minimal respiratory depression with Fluothane on opening the peritoneal cavity.

At present it is not possible to be dogmatic about the relative merits of these and similar techniques and further research is needed in relation to the problem of anoxia. One thing seems to be emerging, namely, that the dangers of high tensions of carbon dioxide appear to have been over-emphasized. This is not to be taken to mean that there is no danger or disadvantage in conducting anaesthesia with a technique allowing high tensions of carbon dioxide. Several workers[10,11] have given evidence of hypercarbia during anaesthesia, particularly with spontaneous respiration, but the writer has seen no evidence that harm has resulted within the ranges studied, for example, under 50 mm. Hg carbon dioxide tension; however, changing the state from one of hypercarbia to one of acapnia in a short period of time may be dangerous.[12]

Certain anaesthetic techniques predispose to anoxia: deep anaesthesia with any agent, and the hypotensive technique with ganglion blocking drugs, especially when this is combined with the anti-Trendelenburg position. This technique is not one for the novice and demands extra skill and care; with these hypoxia can be avoided. Techniques such as hypothermia or the extracorporeal circulation are specifically designed to reduce the hypoxic hazard.

The immediate postoperative period is one of potential danger for the patient. After a prolonged administration of nitrous oxide and oxygen the alveolar concentration of nitrous oxide may rise to produce "diffusion" anoxia; the administration of oxygen at this stage will prevent it. The provision of special accommodation and an adequate and competent staff with the necessary equipment is a responsibility which no hospital can ignore, because these measures will undoubtedly reduce hypoxic and many other hazards immediately following surgical operations.

The growth and recognition of the specialty of anaesthesia will eventually make it possible, because of better agents, better techniques, improved aids for measurement, and more organized facilities, to have effective training programmes for anaesthetists and also for all those who come into contact with unconscious patients. In such ways the hypoxic hazard should decline to the barest minimum.

Acknowledgment

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REFERENCES

1. Courville, C. B. Untoward Effects of N_2O Anaesthesia. California: Pacific Press (1939).
2. Saklad, M. Inhalation Therapy and Resuscitation. Springfield, Ill.: Charles C. Thomas (1953).
3. Comroe, J. H., Jr., & Dripps, R. D. The Physiological Basis for Oxygen Therapy. Springfield, Ill.: Charles C. Thomas (1950).
4. Harris, J. E. Curr. Res. Anesth. *33*: 398 (1954).
5. Comroe, J. H., Jr., & Botelho, S. Amer. J. Md. Sc. *214*: 1 (1947).
6. Beecher, H. K., & Todd, D. P. Ann. Surg. *140*: 2 (1954).
7. Hunter, A. R. Brit. Med. J. *ii*: 919 (1956).
8. Gray, T. C. In Evans & Gray, General Anaesthesia, *1*: 428. London: Butterworth (1959).
9. Marrett, R. Anaesthesia *14*: 28 (1959.)
10. Harbord, R. P. Anaesthesia *10*: 34 (1955).
11. Lucas, B. G. B., & Milne, E. H. Thorax. *10*: 354 (1955).
12. Brown, E. B., Jr., & Miller, F. Amer. J. Physiol. *169*: 56 (1952).

OBSERVATIONS ON PULMONARY CIRCULATION DURING LIGHT ETHER ANAESTHESIA IN MAN*

GORDON M. WYANT, F.F.A.R.C.S., HARRY V. DONALDSON, M.D., AND JOHN E. MERRIMAN, F.R.C.P.(C)†

INVESTIGATIONS carried out during recent years have shed increasing light on the peripheral cardiovascular and respiratory effects of anaesthetic agents and techniques. By comparison much less information is available on the role of the pulmonary circulation in human haemodynamics and the effect of anaesthesia upon it.

Until Cournand proved the ease and efficacy of cardiac catheterization, no method was available for the study of the lesser circulation that could be readily and safely applied in man. Many workers have stressed the importance of the pulmonary circulation in human haemodynamics but their conclusions have been based on either animal experiments or deductions from observations of the systemic circulation.

Johnson's study[1] of the effect of various anaesthetic techniques on the total circulatory system and on respiration was a monumental piece of work. He demonstrated for the first time by direct methods the importance of the lesser circulation and the role of the lung as an important blood depot in man. His studies were made on surgical patients of both sexes in whom age, height, and weight varied greatly, however, and some of whom suffered from cardio-respiratory disability.

Sancetta and Lynn's work[2,3] on spinal anaesthesia was excellent in that the subjects were given no vasopressors and they did not undergo operation. This may explain some of the minor differences in results of their work from that of Johnson. Li and Etsten[4] investigated the haemodynamic effects of cyclopropane and found that pulmonary artery pressure rose during anaesthesia.

In the course of some previous studies of the cardiovascular effects of halothane and of the azeotropic mixture of halothane and ether,[5,6] it had been observed that, as anaesthesia progressed, there was an increase in pulmonary artery pressure and an even more pronounced rise in total pulmonary resistance. Because of a number of variables in this study, such as changing depth of anaesthesia and the use of a new anaesthetic agent of relatively poorly understood properties, it was decided to investigate this phenomenon further and attempt to elucidate what changes occurred in the pulmonary circulation under more controlled conditions of anaesthesia.

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METHOD

Experiments were carried out on 16 healthy male volunteers between the ages of 21 and 30 years. They weighed between 140 and 190 lb. with a mean body surface area of 1.8 square meters. The men were instructed not to have breakfast on the day of the experiment. No medication other than intravenous atropine sulphate was administered. This was given because the study was to be undertaken under light ether anaesthesia and excessive salivation had to be prevented. A cardiac catheter was passed under fluoroscopic control from the left median antecubital vein into the pulmonary artery. An 18 gauge Cournand needle was inserted into the left femoral artery. Electrocardiographic and electroencephalographic leads were applied.

Cardiac Output

Cardiac output was determined by the indicator-dilution technique using the intravenous injection of Cardio-green with arterial sampling through a cuvette oximeter. This method has been described previously in detail.[7]

Peripheral Artery Pressure

By means of the indwelling arterial needle, continuous arterial pressure tracings were recorded. The intra-arterial needle was connected by a polyethylene catheter to a Statham strain gauge and hence to a multi-channel photographic recorder which allowed continuous monitoring and recording of these pressures.

Pulmonary Artery Pressure

The same recording apparatus was used for pulmonary artery pressure as for the peripheral artery pressure, by connecting the cardiac catheter in a similar manner to a strain gauge.

Electrocardiogram

A third channel of the recorder was used for the continuous monitoring and recording of the electrocardiogram.

Electroencephalogram

Tracings were taken at intervals during the experiments on an Edin Anesthograph in order to maintain the depth of ether anaesthesia as nearly constant as possible.

Airway Pressure

Through a special adaptor on the endotracheal connector, a small polyethylene tube was inserted into the airway through the lumen of the endotracheal tube and was connected to a Statham transducer which then allowed airway pressure to be recorded on another channel of the recorder.

Total Peripheral Resistance

This was calculated according to the standard formula:

$$R = \frac{BA\ (FA)_m - O}{CO} \times 1332$$

where R equals the total peripheral resistance in dynes/sec./cm.$^{-5}$, $BA(M)$ or $FA(M)$ is brachial or femoral arterial mean pressure in mm. of mercury, CO represents cardiac output in ml. per sec., O is an approximation of the left ventricular end-diastolic pressure, and 1332 is a figure for the conversion of pressure to dynes.

Total Pulmonary Resistance

This was calculated by using the same formula, substituting pulmonary mean arterial pressure in ml. of mercury for femoral mean artery pressure.

Mean Transit Time

This was calculated from the formula:

$$M.T.T. = \frac{\Sigma\, ct}{\Sigma\, c}$$

c being the concentration of the dye and t being time in sec.

Central Blood Volume

This was calculated according to the formula: "Cardiac output in L./min. × mean transit time/min."

Stroke Volume

Stroke volume was obtained by dividing the calculated cardiac output by the pulse rate which was available from the electrocardiographic tracing.

Control values were recorded over a period of not less than 10 min. and until at least two control cardiac output measurements closely similar to one another were obtained. Anaesthesia was then induced with 2.5 per cent sodium thiopental. This was followed by a dose of succinylcholine and, following inflation of the lungs with oxygen, the throat, larynx, and trachea were sprayed with up to 2 ml. of 4 per cent lidocaine. A No. 9 Magill cuffed endotracheal tube was then passed and this was connected to a Heidbrink anaesthesia machine. Anaesthesia was continued with a mixture of nitrous oxide (4 L.), oxygen (2 L.), and diethyl ether. Clinically, the level of anaesthesia was the lightest consistent with smooth anaesthesia and with tolerance of the endotracheal tube. As soon as anaesthesia had become stabilized, the endotracheal polyethylene catheter was connected to the pressure transducer and measurements of airway pressure were started. It was assumed that the effect of thiopental had worn off when the blood pressure, following the postinduction drop, had become restabilized and the effect of succinylcholine was deemed to have worn off when adequate spontaneous ventilation had become re-established.

After at least a further 10 min. of stable anaesthesia on adequate spontaneous respiration, a cardiac output determination was made and systolic, diastolic, and mean pressures were recorded.

Following completion of these determinations, respiration was actively controlled by means of an Etsten hand ventilator which delivered predetermined tidal volumes. The rate was kept constant by the watch and pressures of inflation were maintained by observing the pressure dial on the machine and also the airway pressure recording on the oscilloscope. Care was taken that the airway pressure returned to base-line during the expiratory pause (Fig. 1).

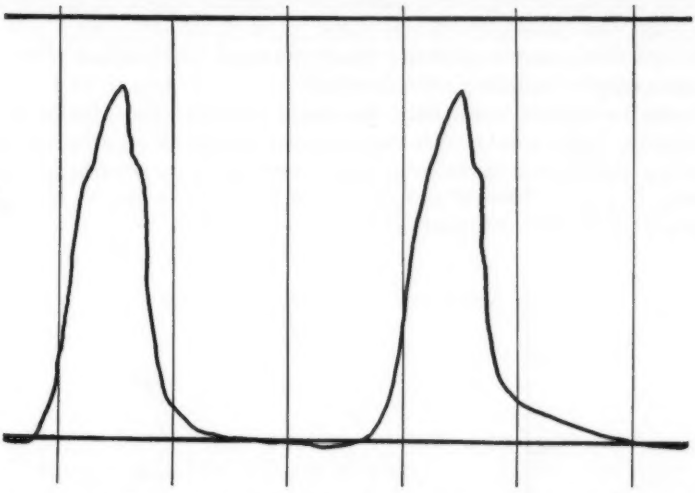

FIGURE 1. Typical airway pressure tracing during controlled respiration with Etsten Ventilator. Base-line: 0 mm./Hg; top-line: 10 mm./Hg; interval between vertical lines: 1 sec.

Non-rebreathing valves only were used. The amount of ether was adjusted to maintain a level of anaesthesia comparable with the one observed during spontaneous respiration. At the end of 10 min., a cardiac output determination was made once more. All means were determined and various other parameters recorded.

Other Determinations

Arterial oxygen percent saturation, $PaCO_2$, and pH were done simultaneously with each cardiac output determination during the first 6 experiments.

In addition to the above 16 experiments, 7 more were done following the same method but intubation was deferred until readings had been obtained on stable anaesthesia with a face mask. At the time of each cardiac output determination, an attempt was made to measure the "pulmonary capillary" pressure by wedging the cardiac catheter in a small branch of a pulmonary artery. Pressures obtained were not used in analysis unless the pressure

could be verified as being a true wedge pressure. The following criteria were met in each case: (i) an atrial type pressure tracing; (ii) lower mean pressure than the mean pulmonary artery pressure; (iii) a sudden unwedging on withdrawal of the catheter; (iv) 100 per cent saturation of a blood sample taken from the site of the catheter tip. Hellems, Haynes, and Dexter[8] have shown that the verified "PC" pressure, meeting the criteria mentioned above, is a true reflection of the mean left auricular pressure. This measurement of "PC" pressure along with the measurements of mean pulmonary artery pressure and cardiac output allowed a partitioning of the total pulmonary resistance into that owing to the pulmonary vascular resistance and that owing to the resistance caused by the left heart.

In a further 3 cases, anaesthesia was maintained with nitrous oxide-oxygen-thiopental drip for purposes of comparison.

In order to exclude mechanical resistance as influencing results several of the subjects, while awake and resting, were made to breathe through the anaesthetic circuit with the endotracheal connector as the mouthpiece and with a noseclip in place. This test was conducted for variable lengths of time while pulmonary pressures were monitored.

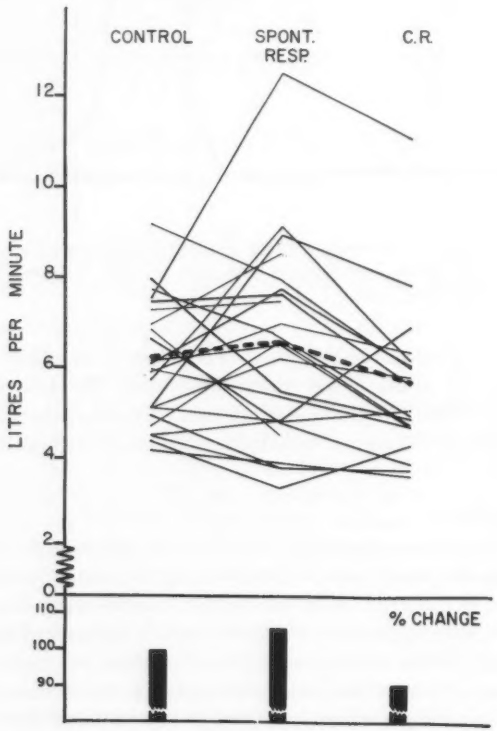

FIGURE 2. Cardiac Output: controlled respiration on Etsten Ventilator.

A number of observations were made using a mechanical ventilator with different pressure curves. Since this part of the investigation is as yet incomplete, it will not be reported here.

Results

Cardiac Output (*Figure 2*)

From observation of this figure, it is at once obvious that there was wide variation of the control cardiac output from individual to individual, each thin line representing a different volunteer. Calculation of the cardiac index did not narrow this scatter, the range being 1.98 to 6.63 with a mean of 4.08.

The response of cardiac output depends upon the depth of anaesthesia, the agent used, and the mean airway pressure.[4, 9, 10, 11, 12] While in some cases in this study there was a considerable increase, analysis of the mean (broken line) revealed statistically insignificant changes in cardiac output. The bottom of the table shows the percentage changes after having assigned arbitrarily the value 100 per cent to all mean controls. This again revealed that the percentage changes are not significant. This is in agreement with Johnson's findings under light ether anaesthesia.

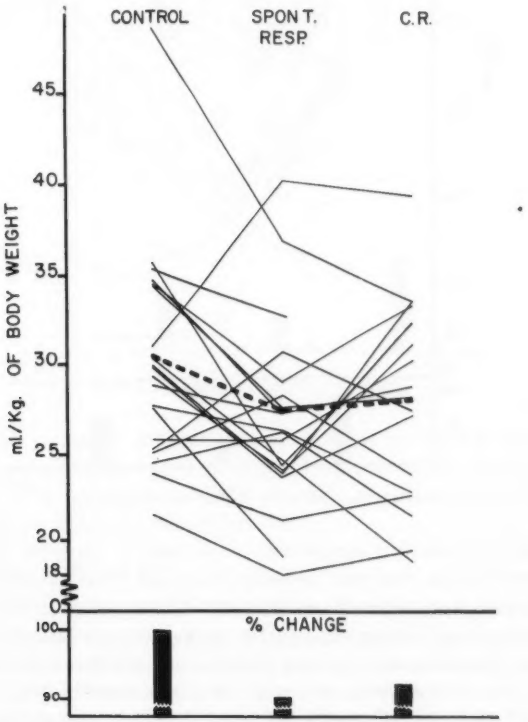

FIGURE 3. Central blood volume.

Central Blood Volume (*Figure 3*)

The mean central blood volume followed closely upon the cardiac output or rather the output followed the central blood volume, except during spontaneous respiration. Here the decrease in central blood volume was significant, although cardiac output and stroke volume were not significantly altered.

Mean Systemic Blood Pressure (*Figure 4*)

This showed the same wide variation of control values as did the other parameters. After anaesthesia had become established, there was usually, but not invariably, a fall of mean systemic pressure with a tendency to some

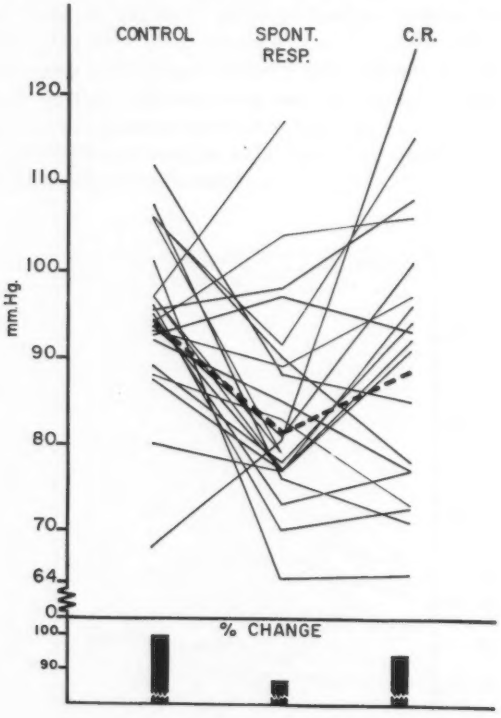

FIGURE 4. Mean systemic blood pressure.

recovery during controlled respiration. The mean (broken line) indicates a quite substantial fall in systemic pressure following establishment of anaesthesia and this difference is statistically significant. There tended to be partial recovery during controlled respiration. The fall in systemic pressure during anaesthesia is a well-known phenomenon and has been previously described in the literature. Nevertheless, it was surprising to realize that this too did not occur invariably. It may be well to record that the subjects in whom the expected fall did not

materialize are different individuals from those whose cardiac output increased rather than fell.

Peripheral Resistance (*Figure 5*)

No significant change was observed in the mean peripheral resistance and it must therefore be deduced that no marked vasodilatation occurs under light ether anaesthesia under the conditions of this experiment. Since there was

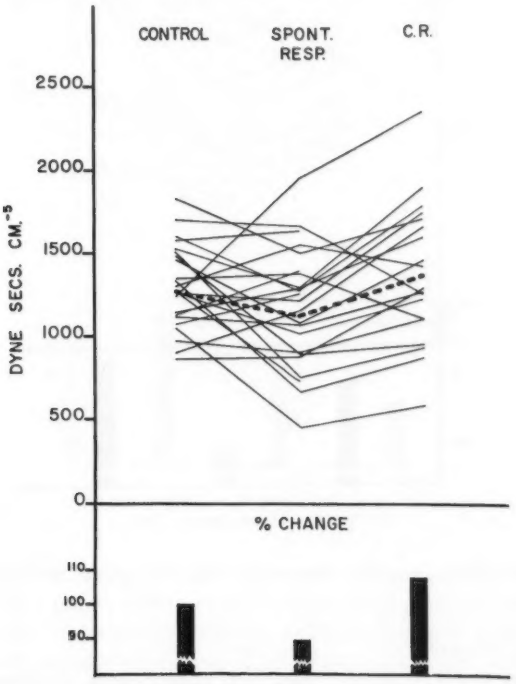

FIGURE 5. Total peripheral resistance.

no significant drop in either cardiac output or total peripheral resistance, one would expect no significant change in mean systemic blood pressure, but this was not the case. The summation of the two has obviously produced a significant change in mean systemic blood pressure.

Mean Transit Time (*Figure 6*)

There was a speeding up of the circulation during spontaneous respiration under anaesthesia followed by slowing under controlled respiration. However, the changes were statistically not significant and therefore it may be said that anaesthesia of the depth used in these experiments does not significantly influence this parameter. It is interesting that, in all but six instances,

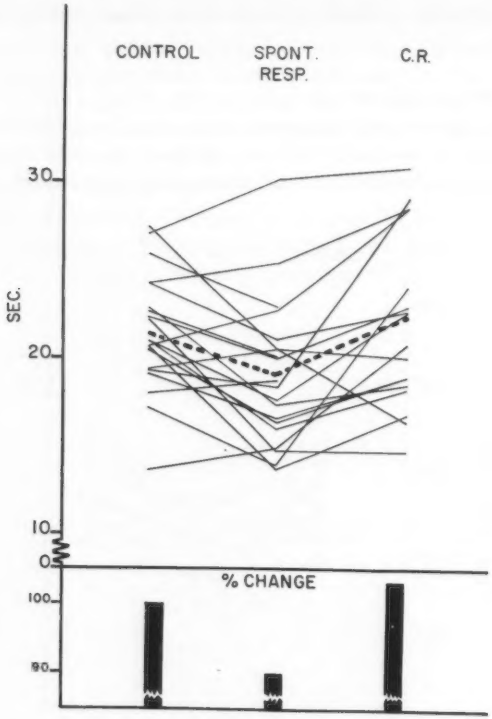

FIGURE 6. Mean transit time.

circulation time was actually somewhat shorter after the subject had been anaesthetized.

Stroke Volume (*Figure 7*)

Although the cardiac output was not significantly depressed or changed while under controlled respiration, the mean value for stroke output was significantly decreased. In other words, cardiac output was maintained by an increase in heart rate. In each individual case in which the stroke output was decreased, there was a concomitant decrease in the calculated central blood volume.

Mean Pulmonary Artery Blood Pressure (*Figure 8*)

There was a relatively wide variation of mean pulmonary blood pressure in the controls. Under spontaneous respiration during ether anaesthesia there was a consistent rise in mean pulmonary artery pressure with the exception of two cases, while in the third no change occurred. As soon as respiration was manually controlled, a further rise in pulmonary artery pressure occurred in all but four instances. This was despite the fact that the system incorporated a non-

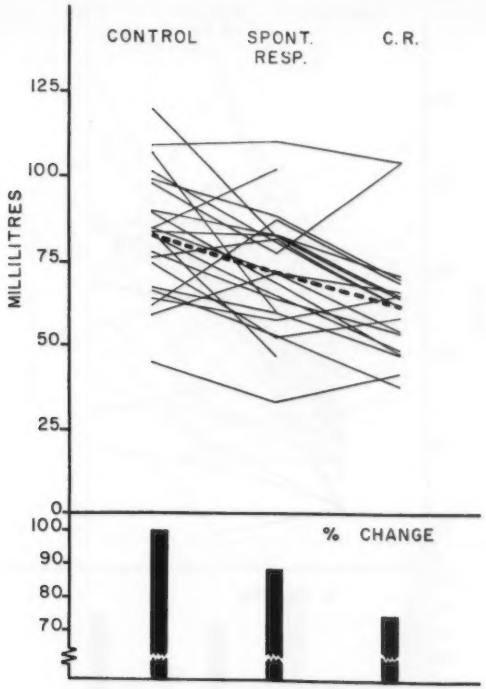

FIGURE 7. Stroke volume.

rebreathing valve and that great care was taken that respiration was slow with adequate expiratory pause and that the endotracheal pressure always returned to the zero baseline. There was thus no positive pressure maintained in the airway during the expiratory pause. The mean pulmonary pressures showed a very marked rise with spontaneous respiration as compared to the control and a further rise while controlled respiration was carried out. These changes are statistically significant.

Total Pulmonary Resistance (*Figure 9*)

The observations made during previous experiments were again confirmed. A significant and continuous rise of the total pulmonary resistance occurred, which increased with spontaneous respiration and further increased when respiration was controlled. It should be remembered at this point that one is dealing with total pulmonary resistance which represents not only the resistance across the pulmonary vascular bed but also the resistance to inflow of blood into the left heart. Therefore, it became imperative to determine which of the two components was primarily responsible for the rise in total pulmonary resistance.

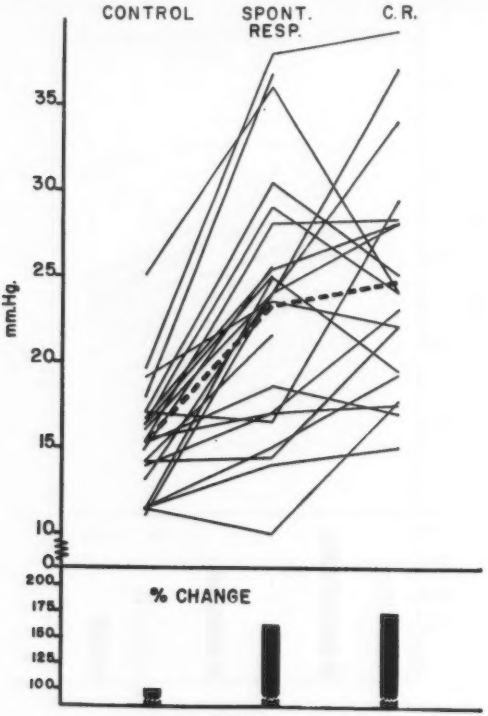

FIGURE 8. Mean pulmonary blood pressure.

In one instance acetylcholine was injected into the pulmonary artery via the cardiac catheter both with the patient awake and resting and after anaesthesia had been induced. Although this produced a fall in peripheral pressure, it did not influence the mean pulmonary pressure or pulmonary resistance. This does not necessarily exclude a theory of pulmonary vasoconstriction since the effect of ether may have predominated over the effect of acetylcholine.

Consequently, it was then decided to measure wedge pressure in a number of experiments. Table I shows the pulmonary artery pressure and the portions thereof due to pulmonary arteriolar resistance and resistance to left auricular filling. It shows the pulmonary hypertension of similar magnitude both with the patient intubated and not. Column 5 shows values obtained after extubation and discontinuation of ether. These figures show that the pressure does not return to control values even though the patients were almost awake. Column 4 illustrates the various pressures while respiration is being controlled. Table II shows the total pulmonary resistances and the two components of it and would indicate the total resistance is more a function of arteriolar resistance than left heart resistance; except during controlled respiration when these values

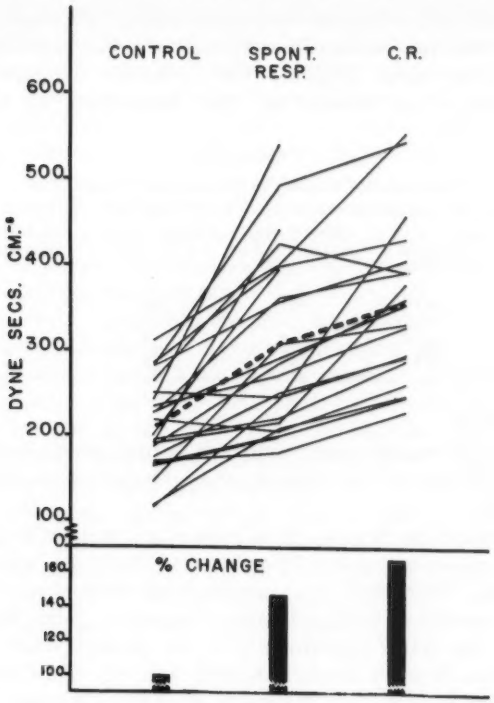

FIGURE 9. Total pulmonary resistance.

TABLE I

COMPONENTS OF PULMONARY BLOOD PRESSURE

	Control	Spont. resp. without tube	Spont. resp. with tube	Etsten ventilator	Extubated
Arterial Pressure	7.1	13.5	13.1	6.5	10.2
Venous Pressure	8.2	11.2	12.3	17.2	12.7
Total Pulmonary Pressure	15.3	24.6	25.4	23.7	22.9

TABLE II

COMPONENTS OF TOTAL PULMONARY RESISTANCE

	Control	Spont. resp. without tube	Spont. resp. with tube	Etsten ventilator	Extubated
Vascular Resistance	102.6	160.7	149.4	96.3	109.3
Lt. Atrial Resistance (Venous)	108.1	135.7	149.6	252.3	138.6
Total Pulmonary Resistance	211.0	297.7	301.0	349.0	248.0

were reversed and left auricular resistance vastly increased. This occurred despite the fact that no positive intrathoracic pressure was allowed to persist during the expiratory pause (Fig. 1). This is further illustrated in Table III, which shows percentage changes for the components of total pulmonary resistance.

TABLE III

PERCENTAGE CHANGES IN PULMONARY RESISTANCE

	Control	Spont. resp. without tube	Spont. resp. with tube	Etsten ventilator	Extubated
Pulmonary Vascular Resistance	100	157	146	93	107
Lt. Atrial Resistance	100	127	139	232	128
Total	100	141	143	165	117

Other Determinations

Blood gas and pH studies done with each output determination on the first 6 subjects were all within the normal range. Oxygen saturation was 100 per cent in each case.

Johnson had found an elevated total pulmonary resistance under both light and deep ether anaesthesia and in those having "Narkotal"-curare anaesthesia. Only those under "Narkotal" anaesthesia alone showed no increase in pulmonary artery pressure or total pulmonary resistance. Since the latter had not been intubated, the last 7 experiments in the present series were done first without intubation to see if intubation itself had any effect on the pulmonary pressure. The 7 subjects showed an initial drop in pulmonary artery pressure after induction with thiopental but as the ether was increased and the anaesthesia reached the levels obtained in the previous experiments, pulmonary artery pressure gradually rose to the level seen previously.

In the 3 other subjects who received nitrous oxide-oxygen with a supplemental intravenous thiopental drip, there occurred also a pulmonary hypertension and increased total pulmonary resistance. These patients were intubated. From these results and the results obtained by Johnson, it would seem that both ether and endotracheal intubation produced an increased total pulmonary resistance.

When the role on total pulmonary resistance of the anaesthetic circuit was studied, it was found that there was no change in the resting level of pulmonary artery pressure in each case, as the awake subjects breathed through the anaesthetic circuit.

SUMMARY AND CONCLUSIONS

Changes in the peripheral circulation under light ether anaesthesia were much less dramatic then in the pulmonary circulation. The only changes observed were in a reduction of the mean systemic blood pressure and of the stroke volume. Central blood volume was decreased only during spontaneous respiration. Changes in the pulmonary circulation, on the other hand, were quite remarkable in that both mean pulmonary artery blood pressure and total pulmonary resistance rose as ether anaesthesia became established before

intubation, but a further rise occurred after the tube had been inserted. Thereafter a further rise was noted when respiration was manually controlled. This occurred despite the fact that there remained no positive airway pressure during the expiratory pause. Following extubation the pulmonary artery pressure and total resistance did not return to normal until the subjects were practically awake. Results were not influenced by resistance in the anaesthetic circuit.

From wedge pressure studies it would appear that the increase in total pulmonary resistance on spontaneous respiration is in a larger measure due to the vascular component, whereas during controlled respiration left atrial resistance plays the predominant role.

At this stage of the investigation one is somewhat reluctant to draw practical conclusions from these findings. Further studies must be carried out to determine what effects other anaesthetic agents have on pulmonary circulation. From previous studies it would appear that both halothane and azeotropic halothane-ether behave in a similar fashion but other agents and the role of depth of anaesthesia and of the relaxant drugs must be evaluated. Further studies are also needed with different patterns of ventilation before final conclusions can be drawn. However, the thought must naturally occur that, although the increased total pulmonary resistance observed in these studies may not be of great practical significance in healthy individuals, the strain imposed on the right heart by this increased resistance may become a significant factor indeed in patients with poor cardiac reserve.

Acknowledgment

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Résumé

Nous avons fait des expériences sur 16 jeunes volontaires masculins pour étudier les modifications de la dynamique circulatoire, plus particulièrement la circulation pulmonaire, au cours de l'anesthésie légère à l'éther. Nous avons mesuré et enregistré par moyens directs le débit cardiaque, la pression artérielle périphérique, l'électrocardiogramme et la pression dans les voies respiratoires et nous avons calculé la résistance périphérique totale et la résistance pulmonaire, la vitesse moyenne de circulation, le volume sanguin central et le volume systolique. Le niveau d'anesthésie a été maintenu constant à l'aide de l'électroencéphalogramme. Au cours de certaines expériences, nous avons même étudié le pourcentage de saturation en oxygène du sang artériel, le $PaCO_2$ et le pH. Toutes ces analyses ont été faites, le malade étant éveillé, respirant spontanément après l'intubation mais aidé par le ventilateur manuel Etsten, et de nouveau après l'extubation. Au cours d'un certain nombre d'expériences, nous avons également fait des prélevés alors que les malades respiraient

spontanément avec un masque seulement sur la face. Nous avons mesuré les pressions dans les segments pour étudier la différénce entre les composantes artérielles et veineuses de la pression et de la résistance pulmonaire totale.

A la suite de ces études, nous avons constaté que les seuls changements sur la circulation périphérique, au cours de l'anesthésie légère à l'éther, consistaient en une diminution de la moyenne de la pression sanguine systolique et du volume systolique durant toutes les phases des expériences et du volume sanguin central durant la respiration spontanée. Les changements les plus notoires, d'autre part, ont été observés sur la circulation pulmonaire et ont consisté en ce que la moyenne de la pression sanguine dans l'artère pulmonaire et la résistance pulmonaire totale se sont élevées toutes les deux durant l'induction de l'anesthésie à l'éther, elles se sont élevées encore davantage après l'intubation et encore davantage au cours de la respiration contrôlée. Après l'extubation, la pression dans l'artère pulmonaire et la résistance ne revenaient à la normale seulement lorsque les malades étaient pratiquement réveillés. Grâce à des expériences de contrôle, nous avons pu établir que ces résultats n'étaient pas influencés par la résistance dans les appareils à anesthésie. L'étude de la pression dans les segments laisse comprendre que l'augmentation de la résistance pulmonaire totale, au cours de la respiration spontanée, était due davantage aux composantes vasculaires car durant la respiration contrôlée, la résistance de l'oreillette gauche jouait le principal rôle.

REFERENCES

1. Johnson, S. R. The Effect of Some Anaesthetic Agents on the Circulation in Man. Acta Chirurg. Scandinav. Supp. 158.
2. Sancetta, S. M.; Lynn, R. B.; Simeone, F. A.; & Scott, R. W. Studies of Haemodynamic Changes in Humans Following Induction of Low and High Spinal Anaesthesia. Circulation *6* (4): 559-571 (1952).
3. Lynn, R. B.; Sancetta, S. M.; Simeone, F. A.; & Scott, R. W. Observations on the Circulation in High Spinal Anaesthesia. Surgery. *32* (2): 195-213 (1952).
4. Li, T.-H., & Etsten, B. Effect of Cyclopropane Anesthesia on Cardiac Output and Related Haemodynamics in Man. Anesthesiology. *18* (1): 15-32 (1957).
5. Wyant, G. M.; Merriman, J. E.; Kilduff, C. J.; & Thomas, E. T. The Cardiovascular Effects of Halothane. Canad. Anaesth. Soc. J. *5* (4): 384-402 (1958).
6. Wyant, G. M.; Merriman, J. E.; Harland, J. H.; & Donaldson, H. V. The Cardiovascular Effects of Azeotropic Halothane-Ether. Canad. Anaesth. Soc. J. *7* (2): 91-99 (1960).
7. Merriman, J. E.; Wyant, G. M.; Bray, G.; & McGeachy, W. Serial Cardiac Output Determinations in Man. Canad. Anaesth. Soc. J. *5* (4): 375-383 (1958).
8. Hellems, H. K., Haynes, F. W., & Dexter, L. Pulmonary Capillary Pressure in Man. J. Appl. Physiol. *2* (1): 24-29 (1949).
9. Cathcart, R. T.; Nealson, T. F., Jr.; Fraimow, W.; Hamptom, L. J.; & Gibbon, J. H., Jr. Cardiac Output Under General Anaesthesia: Effect of Mean Endotracheal Pressure. Ann. Surg. *148* (3): 488-497 (1958).
10. Etsten, B., & Li, T. H. Hemodynamic Changes During Thiopental Anesthesia in Humans: Cardiac Output, Stroke Volume, Total Peripheral Resistance, and Intrathoracic Blood Volume. J. Clin. Invest. *34*: 500 (1955).
11. Lee, G. De J.; Churchill-Davidson, H.; Miles, B. E.; & De Wardener, H. E. Circulatory Effects of Prolonged Light Anaesthesia In Man. Clin. Sc. *12*: 169 (1953).
12. Shackman, R., Graber, I. G., & Melrose, D. G. Haemodynamics of Surgical Patient under General Anaesthesia. Brit. J. Surg. *40*: 193 (1952).

UNUSUAL RESPONSES TO DRUGS IN SOME HEREDITARY CONDITIONS*

W. KALOW, M.D.†

AN UNUSUAL RESPONSE to a drug may have disastrous consequences, or may be a mere nuisance, but—if studied systematically—unusual responses offer new insight into the normal mode of action of drugs. One may facilitate such a systematic study by dividing unusual drug responses into two large categories: those arising from external influences, and those caused by hereditary conditions. At the present state of knowledge, it is not always possible to divide drug reactions in this manner but clear-cut examples of such external factors are death due to atropine in hot weather[1] when interference with perspiration may cause heat stroke[2] or, as has been recently claimed, an increased risk of general anaesthesia after exposure to radiation.[3] The purpose of the present paper is to give examples of drug reactions which have in common that they obey the rules of heredity; application of these rules will gradually reduce some elements of surprise in the use of drugs and thereby increase their safety.

The following discussion will deal mostly with drugs of some concern to anaesthetists and it should be kept in mind that genetically determined deviations from a usual drug response occur in organisms of all kinds. Resistance of bacteria to penicillin develops if there are a few individual organisms in a colony which are resistant to this antibiotic and which get a chance to spread and multiply if the colony is exposed to penicillin.[4] In a similar way, the resistance of insects to insecticides is evidence for genetically determined variations in the response to these agents.[5] Some strains of mice are more susceptible to the toxic action of pentobarbital than other strains, and these differences between strains are heritable.[6] Some rabbits have, and others lack, the enzyme atropine esterase;[7] those which have the enzyme show fleeting effects of atropine.[8] Of the heritable influences on drug response in man, I want to mention only two which affect anaesthesia indirectly. First, some types of haemolytic reaction from coal tar analgesics, sulphonamides, or antimalarials like primaquin are due to an inherited enzymatic defect in red cells.[9] This defect occurs in Negroes more often than in Caucasians. Second, the antituberculous drug isoniazid is metabolized by some people faster than by others;[10] those who do not readily metabolize the drug are prone to develop a secondary vitamin B_6(pyridoxine) deficiency,[11] a deficiency which may find expression in various neurological disorders. The hereditary determination of isoniazid metabolism has been established recently.[12]

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We will now turn to some drugs used in anaesthesia. The outcome may be very serious if barbiturates are administered to patients suffering from porphyria.[13, 14] There are several forms of porphyria;[15] most important is the acute intermittent type of this disease.[14] We still do not know its biochemical cause but research of the past 15 years has eliminated the misconception that porphyrins are poisonous breakdown products of heme. The work of Rimington, Waldenström, Shemin, Gibson, Granick, and many others has conclusively shown that porphyrins are precursors of heme.[16, 17] It appears likely that the metabolic error in porphyria involves some of the simple biochemical building stones, namely acetic acid and glycine. Proper utilization of these agents for heme synthesis requires oxidative phosphorylation which can be blocked by barbiturates.[18] A derangement of this or another similarly fundamental biochemical event is probably responsible for the initiation of a porphyric attack. Metabolic products which appear in human urine during a porphyric attack are often precursors of porphyrins, rather than porphyrins themselves. The porphyrins have a red colour and can, therefore, be seen in urine, but the pre-

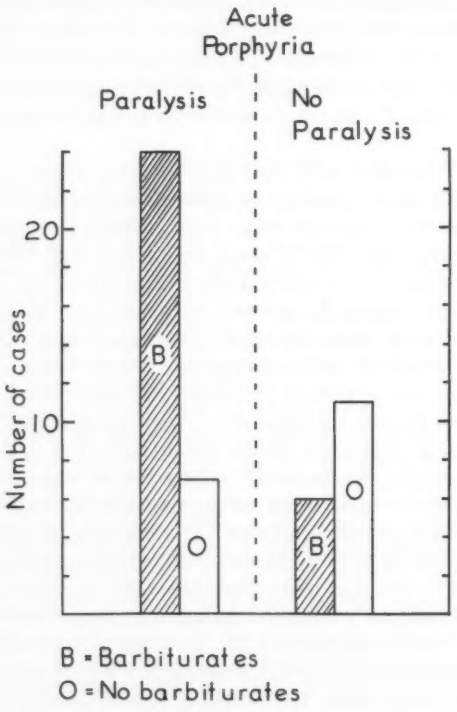

FIGURE 1. The relationship between barbiturate administration and the onset of paralysis in 48 patients with acute intermittent porphyria. (Data of A. Goldberg, 1959.)

cursors are colourless. Fortunately, porphobilinogen can be demonstrated with a very simple laboratory test.[19] Anatomical lesions of porphyria may consist in patchy demyelination which may be related to autonomic symptoms, to paralysis of motor nerves, and to mental disturbances.[14] A fairly consistent sign is a rapid heart rate, often combined with hypertension. The presenting symptom is frequently abdominal pain of such severity that surgery seems indicated. Under these circumstances thiopental may change the character of the attack and produce paralysis,[14, 20] which may be fatal by interference with respiration or, if not fatal, may cause a patient to be bedridden for periods of weeks and perhaps months. Not all persons with the hereditary defect develop clinical symptoms. Thus the disease may not be evident in every carrier of the gene; yet one gene is sufficient to produce the disease, that is, inheritance is dominant.[21]

Another hereditary condition which affects the practice of anaesthesia is the occurrence of atypical pseudocholinesterase in the serum of some persons.[22] This unusual enzyme does not seem to cause any disease but it fails to hydrolyse succinycholine in clinical concentrations,[23] so that the relationship between relaxant dose and duration of action is quite different in persons with atypical esterase and in those with the usual type of enzyme. In a sense, it is wrong to speak of a prolonged apnoea after succinylcholine, if a person has atypical esterase; the long duration of action is a predictable, reproducible, and thus regular occurrence. With proper artificial respiration the patient also seems to

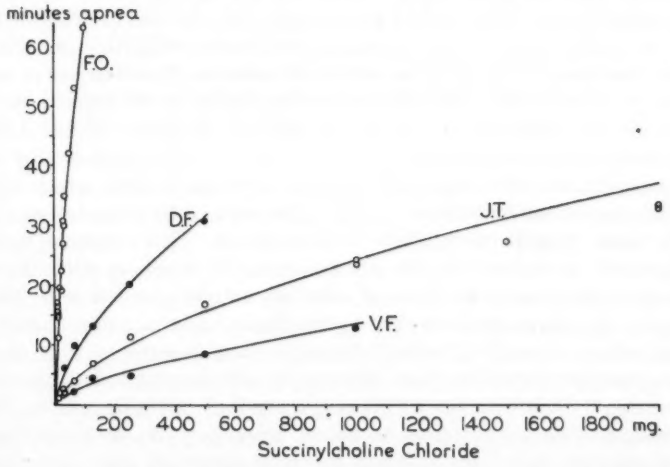

FIGURE 2. Relation between dose of succinylcholine chloride and duration of apnoea in 4 representative patients. Various doses were administered at intervals of days or weeks for electroshock treatment.

Patient V.F. represents a case with a high level of usual type of esterase; Patient J.T., low level of usual type of esterase; Patient D.F., mixture of normal and atypical esterase with preponderance of the latter; Patient F.O., atypical esterase. (Data of Kalow and Gunn, 1957.)

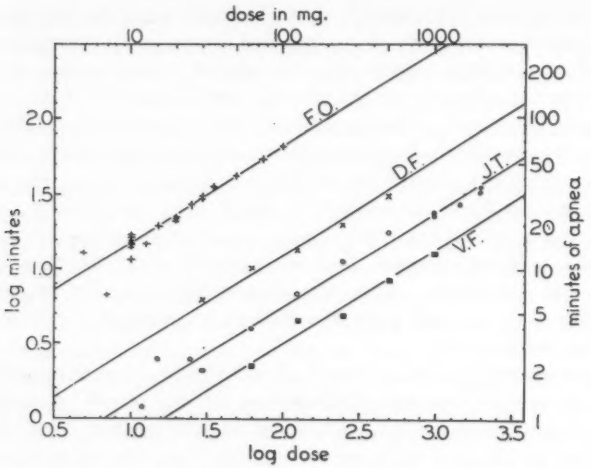

FIGURE 3. Same data as in Figure 2 on a logarithmic plot. (Figure by Kalow and Gunn (1957) reproduced with permission of the J. Pharmacol. & Exper. Therap.)

be quite safe after succinylcholine even if one has to wait for a few hours until the drug effect is over. One cannot get a short action of succinylcholine in these patients since they need 10 mg. of succinylcholine for relaxation and since even this small dose can be expected to act for 10 minutes. It is important to appreciate that equipment for artificial respiration ought to be immediately available, even if one administers only a test dose of the drug. About 1:2,000 or 3,000 patients have the atypical esterase;[24] much more frequent are persons who have a mixture of normal and atypical esterase in their serum. They are the heterozygotes and constitute nearly 4 per cent of the population. There is clinically little trouble with these heterozygotes. Their plasma hydrolyses succinylcholine at about half the normal rate. In a person with the normal type of cholinesterase, reduction of esterase activity to one-half normal in the presence of cancer or liver disease[25] is likely to be accompanied by some prolonged effect of succinylcholine unless the dose is reduced. One must consider the possibility that the liver damage as such may influence the duration of drug action by some means which is independent of cholinesterase. I should like to mention that any attempt to detect heterozygosity by simple measurements of reaction rate[26] does permit the recognition of not more than two-thirds of the heterozygotes.[27]

In hypokalemic hereditary periodic paralysis, attacks have been induced by glucose, insulin,[28] or chlorothiazide.[29] There is, however, a very rare hyperkalemic form of this disease in which anaesthesia appears to precipitate severe paralysis.[30] For example, thiopental given for a dental extraction left a patient unable to move for several hours after awakening. Similar attacks have occurred

in two women after childbirth under anaesthesia; one of the women delivered another child with spinal anaesthesia without sustaining an attack.

An inherited anatomical feature[31] which may spell trouble for the anaesthetist is a narrow angle between cornea and iris, that is, a shallow anterior chamber of the eye. This narrow angle is a prerequisite[32] for the primary acute glaucoma, while the simple chronic glaucoma frequently occurs in eyes with a wide angle. A sharp distinction between the glaucomata is necessary since the action of some drugs on intraocular pressure is different in these conditions.[33] During pupillary dilatation, the iris may crowd the drainage canals of the aqueous humour if there is a narrow angle, but not if the angle is wide. Hence the

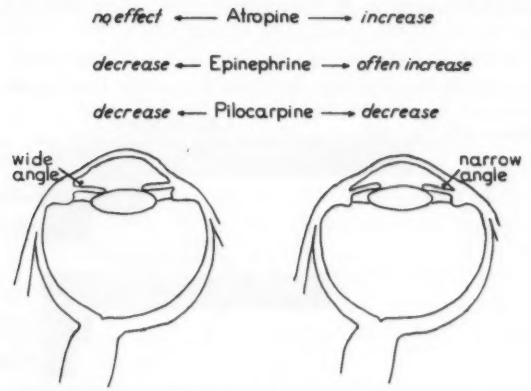

FIGURE 4. Differential effects of drugs on intraocular pressure in narrow-angle and in wide-angle glaucoma. See text for further explanation.

mydriatic action of atropine blocks the drainage with a consequent rise of intraocular pressure in acute glaucoma, but it has little effect on the pressure in simple glaucoma and on a normal eye. Strangely enough, this distinction does not have to be made if the opposite pharmacological effect is sought, since cholinergic stimulation, as, for instance, exerted by pilocarpine, reduces intraocular pressure in any type of glaucoma. On the other hand, adrenergic agents reduce intraocular pressure in simple glaucoma but enhance the pressure in acute glaucoma. This double action has been observed with epinephrine, phenylephrine,[34] ephedrine, and cocaine.[33]

Since epinephrine is frequently liberated during general anaesthesia,[35] this double action may well explain why some observers find that general anaesthetics lower intraocular pressure,[36] and yet glaucomatous attacks have been initiated by general anaesthesia and surgery.[37] In these cases, the attack may be the combined result of preoperative atropine enhancing the pupillary dilatation of deep anaesthesia, and of epinephrine liberation due to anxiety[38] and the action of, for example, ether. Succinylcholine is able to raise the intraocular pressure but this is a relatively minor effect of short duration; the

pressure rises more as a result of intubation than of the drug.[39] If one suspects a narrow-angle glaucoma, a prophylactic drop of 2 per cent pilocarpine preoperatively is indicated.[37]

In short, the relatively frequent, slowly progressing, simple glaucoma of old age is nothing which the anaesthetist has to fear, but this is no reason to neglect the dangers of the relatively rare, acute, narrow-angle glaucoma. The most likely candidates for this latter glaucoma are elderly women. The prodromal stages are characterized by a combination of sporadic headache with the appearance of halos resulting from corneal oedema. A single observation of a normal intraocular pressure does not exclude the presence of the disease. The mode of inheritance seems to be variable but a question for acute glaucoma among relatives of the patient may be worth while.[40]

The colour of the iris is genetically determined. The different content of pigment reflects a difference in biochemical make-up. It is known that irises of

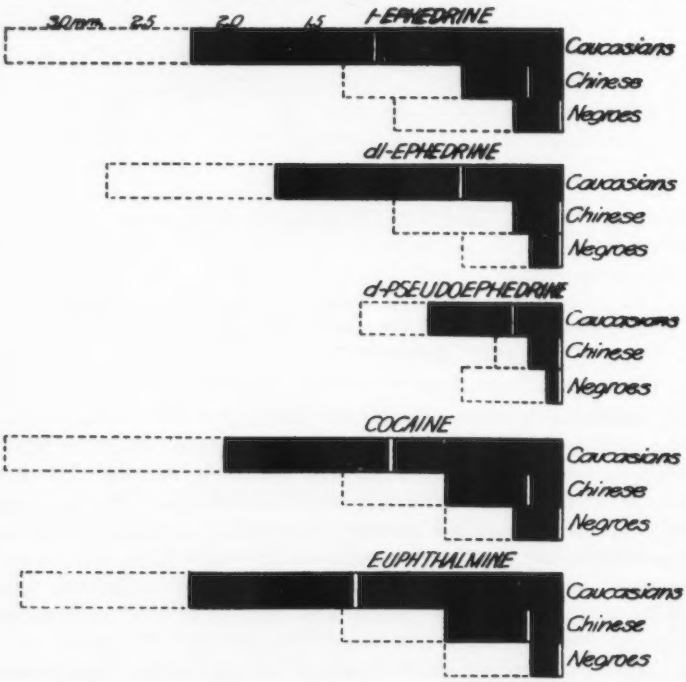

FIGURE 5. Comparison of the mydriatic action of 1-ephedrine, dl-ephedrine, d-pseudoephedrine, cocaine, and euphthalamine in Caucasians, Chinese, and Negroes. Each scale expressed in millimeters represents the results of 10 subjects. The solid scaledenotes the average increase of the transverse diameter of the pupil. The solid scale plus that enclosed in the broken lines indicates the maximum value in the series, and that portion of the solid scale on the right side of the white vertical line the minimal value in the same series. (Reproduced by permission of K. K. Chen and the J. Pharmacal. & Exper. Therap.)

different colour contain different activities of dopa oxidase.[41] While not all the biochemical relationships are understood, there is no doubt that eyes of different colour react with different intensity to mydriatic agents. This has been shown for rabbit eyes[41] but it holds for human eyes as well.[42, 43] K. K. Chen, who with Carl F. Schmidt introduced the Chinese drug ephedrine into Western medicine, found that sympathomimetic drugs including cocaine had a strong mydriatic effect on European eyes, a moderate effect on Chinese eyes, and practically no effect on Negro eyes.[44] It is very likely that this reflects a different metabolism of aromatic amines, including epinephrine. In this connection it is interesting to note the observation of an Australian dentist, Dr. Sutton, who claims that persons with dark eyes are more susceptible to pain than persons with light eyes.[45] The contents of his article, plus comments, were published as an Editorial in the British Medical Journal,[46] which initiated quite a flow of letters. The possibility of an indirect though real connection between eye colour and such a complex function as pain, should be investigated on a biochemical, not emotional, basis. There are several examples in biochemical genetics of a relation between pigmentation and other factors. For instance, the atropine esterase in rabbits is genetically linked with fur colour.[7] Genes which affect the colour of mouse hair are known at at least twenty-four different loci; at eight of these loci are genes with highly specific effects on other characters.[47] In human beings, the metabolic error of phenylketonuria causes mental deficiency accompanied by light eyes and blond hair. I wonder whether there is any truth in the old tale that red-haired patients tend to bleed excessively during surgery?

There have been reports from the United States,[48, 49] Jamaica,[50] Africa,[51] and the Fiji Islands,[52] stating that the operative mortality of persons with dark skin pigmentation is greater than those with light skin. Circulatory collapse seems to play a major role in this morality. Efforts have been made, particularly in Jamaica, to sort out the various responsible factors. Persons of African descent showed regularly a high rise of blood sugar during an operation, which indicates an excessive response of the adrenal medulla;[53] on the other hand, the adrenal cortex was found to be anatomically small[54, 55] and the urinary excretion rate of 17 ketogenic steroids to be low.[56] One may speculate that this adrenal imbalance in conjunction with the low blood volume characteristic of undernutrition is the cause of the fatal collapse. In any case, there are probably both genetic and environmental factors in operation, the relative importance of which is still to be elucidated.

The cases mentioned indicate the diversity which hereditary influences may have on the response to drugs. Some of the conditions described are rather rare; one may raise the question, why bother with such rarities—yet the study of exceptions is the best means of recognizing ordinary rules.

Many environmental, non-hereditary, and pathological conditions such as undernutrition, obesity, bleeding, or cardiovascular dysfunction are either obvious or easily revealed by physical examination. The biochemical individuality which affects the response to drugs often tends to be hidden. Yet in view of the serious consequences which may be blindness, paralysis, or even

death, a preoperative question as to unusual drug responses in the family might be worthwhile. If one suspects an hereditary nature of a rare, unusual response to a drug, it is important to find out whether there is a blood relationship between the parents.

One always has to keep in mind that the Gauss-curve, that is the normal, bell-shaped distribution curve of drug response, is often not applicable when one is dealing with unusual drug responses. This has numerous consequences; for instance, the concepts of gene frequency, of genetic polymorphism, and of heterozygous carriers, are likely to assume some new importance. Anaesthetists who are trained to record drug responses in human beings are in a good position to detect a wide variety of hereditary factors which influence the effect of drugs.

REFERENCES

1. JAHNKE, W. Atropinvergiftungen im heissen Klima. Archiv fur Toxicologie *16*: 243 (1957).
2. FORD, W. L. Heat Stroke with Mepazine Treatment. Am. J. Psychiat. *116*: 357 (1959).
3. ZAUDER, H. L., & ORKIN, L. Ionizing Radiation and Anesthetic Risks. Med. Klin. (Berl.) *55*: 239 (1960).
4. POLLOCK, M. R. Drug Resistance and Mechanisms for its Development. Brit. M. Bull. *16*: 16 (1960).
5. BROWN, A. W. A. Insecticide Resistance in Arthropods. W.H.O. (Geneva). Monograph 38 (1958).
6. MCLAREN, A., & MICHIE, D. Variability of Response in Experimental Animals: A Comparison of Reactions of Inbred F_1 Hybrid and Random Bred Mice to a Narcotic Drug. J. Genet. *54*: 440 (1956).
7. SAWIN, P. B., & GLICK, D. Hydrolysis of Atropine by Esterase Present in Rabbit Serum. Proc. Nat. Acad. Sc. *29*: 55 (1943).
8. WERNER, G., & WURKER, R. Untersuchungen zur Mydriasis bei Kaninchen durch (-)-Hyoscyamin. Naturwiss. *22*: 627 (1959).
9. BEUTLER, E. The Hemolytic Effect of Primaquine and Related Compounds: A Review. Blood *24*: 103 (1959).
10. HUGHES, H. B.; BIEHL, J. P.; JONES, A. P.; & SCHMIDT, L. H. Metabolism of Isoniazid in Man as Related to the Occurrence of Peripheral Neuritis. Am. Rev. Tuberc. *70*: 266 (1954).
11. MCCORMICK, D. B., & SNELL, E. E. Pyridoxyl Kinase of Human Brain and its Inhibition by Hydrazine Derivatives. Proc. Nat. Acad. Sc. *45*: 1371 (1959).
12. PRICE EVANS, D. A.; MANLEY, K. A., & MCKUSICK, V. A., Genetic Control of Isoniazid Metabolism in Man. Brit. Med. J. *ii*: 485 (1960).
13. DEAN, G. Porphyria. Brit. Med. J. *ii*: 1291 (1953).
14. GOLDBERG, A. Acute Intermittent Porphyria. A Study of 50 Cases. Quart. J. Med. *28*: 183 (1959).
15. WALDENSTRÖM, J. The Porphyrias as Inborn Errors of Metabolism. Amer. J. Med. *21*: 758 (1959).
16. GRANICK, S., & MANZERALL, D. Enzymes of Porphyrin Synthesis in Red Blood Cells. Ann. N.Y. Acad. Sc. *75*: 115 (1958).
17. LONDON, I. M. Metabolism of the Mammalian Erythrocyte. Bull. N.Y. Acad. Med. *36*: 79 (1960).
18. HUNTER, F. E., & LOWRY, O. H. The Effects of Drugs on Enzyme Systems. Pharm. Rev. *8*: 135 (1956).
19. WATSON, C. J., & SCHWARTZ, S. A Simple Test for Urinary Porphobilinogen. Proc. Soc. Exp. Biol. Med. *67*: 393 (1941).
20. WALDENSTRÖM, J. Porphyrie und Arzneimittel. In Nebenwirkungen von Arzneimitteln auf Blut und Knochenmark. Stuttgart: F. K. Schattauer-Verlag (1957).

21. DEAN, G., & BARNES, H. D. Porphyria in Sweden and South Africa. S. Afr. Med. J. *33*: 246 (1959).
22. KALOW, W. Cholinesterase Types. Ciba Found. Symp. Biochemistry of Human Genetics, p. 39. London (1959).
23. KALOW, W. The Distribution, Destruction and Elimination of Muscle Relaxants. Anesthesiology *20*: 505 (1959).
24. KALOW, W., & GUNN, D. R. Some Statistical Data on Atypical Chloinesterase of Human Serum. Ann. Human Genetics *23*: 239 (1959).
25. WETSTONE, H. J.; LAMOTTA, R. V.; BELLUCCI, A.; TENNANT, R.; & WHITE, B. V. Studies of Cholinesterase Activity. V. Serum Cholinesterase in Patients with Carcinoma. Ann. Int. Med. *52*: 102 (1960).
26. KAUFMAN, L., LEHMANN, H., & SILK, E. Suxamethonium Apnoea in an Infant. Brit. Med. J. *i*: 166 (1960).
27. KALOW, W., & STARON, N. On Distribution and Inheritance of Atypical Forms of Human Serum Cholinesterase, as Indicated by Dibucaine Numbers. Canad. J. Biochem. Physiol. *35*: 1305 (1957).
28. CONN, T. W.; FAJANS, S. S.; LOUIS, L. H.; STREETEN, D. H. P.; & JOHNSON, R. D. Intermittent Aldosteronism in Periodic Paralysis. Lancet *i*: 802 (1957).
29. COHEN, T. Hypokalemic Muscle Paralysis Associated with Administration of Chlorothiazide. J.A.M.A. *170*: 2083 (1959).
30. EGAN, T. J., & KLEIN, R. Hyperkalemic Familial Periodic Paralysis. Pediatrics *24*: 761 (1959).
31. KELLERMAN, L., & POSNER, A. The Value of Heredity in the Detection and Study of Glaucoma. Acta XVII Council Ophth. *2*: 1129 (1954).
32. DUKE-ELDER, S. Parson's Diseases of the Eye, p. 234. 12th ed. London: Churchill (1956).
33. GRANT, W. M. Physiological and Pharmacological Influences upon Intraocular Pressure. Pharm. Rev. *1*: 143 (1955).
34. LEE, P. F. The Influence of Epinephrine and Phenylephrine on Intraocular Pressure. A.M.A. Arch. Ophth. *60*: 862 (1958).
35. PRICE, H. L.; LINDE, H. W.; JONES, R. E.; BLACK. G. W.; & PRICE, M. L. Sympatho-Adrenal Responses to General Anaesthesia in Man, and their Relationship to Haemodynamics. Anesthesiology *20*: 563 (1959).
36. KORNBLUETH, W.; ALADJEMOFF, L.; MAGORA, F.; & GABBAY, A. Influence of General Anaesthesia on Intraocular Pressure in Man. A.M.A. Arch. Ophth. *61*: 84 (1959).
37. GARTNER, S., & BILLET, E. Acute Glaucoma as a Complication of General Surgery. Am. J. Ophth. *45*: 66 8 (1958).
38. CROLL, M., & CROLL, L. J. Emotional Glaucoma. Am. J. Ophth. *49*: 297 (1960).
39. WYNANDS, J. E., & CROWELL, D. E. Intraocular Tension in Association with Succinylcholine and Endotracheal Intubation: A Preliminary Report. Canad. Anaesth. Soc. J. *1*: 39 (1960).
40. SIMMONS, W. D. A Review of the Data on the Occurrence of Glaucoma. Am. J. Ophth. *47*: (2): 62 (1959).
41. ANGENENT, W. J., & KOELLE, G. B. A Possible Enzymatic Basis for the Differential Action of Mydriatics on Light and Dark Irises. J. Physiol. *119*: 102 (1953).
42. SCOTT, T. G. The Eye of the West African Negro: Stronger Mydriatic Drugs. Brit. J. Ophth. *29*: 12 (1945).
43. VENABLE, H. P. Glaucoma in the Negro. J. Nat. M.A. *44*: 7 (1952).
44. CHEN, K. K., & POTH, E. J. Racial Differences as Illustrated by the Mydriatic Action of Cocaine, Euphthalmine, and Ephedrine. J. Pharmacal. & Exper. Therap. *36*: 429 (1929).
45. SUTTON, P. R. N. Association between Colour of the Iris of the Eye and Reaction to Dental Pain. Nature *184*: 122 (1959).
46. EDITORIAL. Steely Eyes and Pain. Brit. Med. J. *ii*: 418 (1959).
47. HALDANE, J. B. S. The Biochemistry of Genetics, p. 66. London: Allen & Unwin (1954).
48. VEAL, T. R., & VAN WERDEN, B. D. Mortality of Spinal Analgesia Based on an Analysis of 30 Immediate Fatalities in a Series of 33,811 Cases. Am. J. Surg. *34*: 606 (1936).
49. TRENT, J. C. & GASTNER, E. Anaesthetic Death in 54,128 Consective Cases. Ann. Surg. *119*: 954 (1944).

50. KEATING, V. J. Anaesthetic Problems in a Tropical Country. Proc. World Fed. Anaesthetists (1955).
51. BARLOW, M. B. Cit. Keating, V. J., Anesthesia *13*: 434 (1958). South African Med. J. (Mar. 21, 1953).
52. PHILLIPS, L. A., & COHEN, R. I. Operative Stress and the Adrenals. Anesthesia *14*: 270 (1959).
53. KEATING, V. J. Carbohydrate Metabolism: The Effects of Surgery in a Tropical Population. Anesthesia *13*: 434 (1958).
54. STIRLING, G. A., & KEATING, V. J. Size of the Adrenals in Jamaicans. Brit. Med. J. *ii*: 1016 (1958).
55. STIRLING, G. A. The Adrenal Glands in Jamaican Infants. J. Path. Bact. *77*: 555 (1959).
56. BLANE, G. F. Urinary 17-Ketosteroids and Ketogenic Steroids in a Mixed Jamaican Population. Lancet *i*: 498 (1959).

THE HALOTHANE-ETHER AZEOTROPE: AN ILLOGICAL MIXTURE

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THE HALOTHANE-ETHER AZEOTROPE was introduced into clinical anaesthesia by Hudon, Jacques, and Boivin[1] in an attempt to counteract the cardiovascular and respiratory effects of halothane. Responsibility for its inception was also claimed by Lott[2] who described it as non-inflammable and suggested that the addition of ether to halothane might diminish what he called the toxicity of the latter drug which, for reasons unspecified, reminded him of chloroform.

The optimal proportions suggested for the azeotrope were 68.3 parts of halothane to 31.7 parts of ether.[3] It was recognized that, although the mixture of the liquids was azeotropic in all proportions, the suggested 2 : 1 ratio (approximately) was safest from the point of view of fire and explosion hazard. It appears to have been assumed that the dose range of the mixture should be similar to that of halothane, that is, 1 per cent to 4 per cent of the vapour v/v in the inspired gases, and this range of concentrations was shown to be non-inflammable in air or oxygen, the lower limit of inflammability being 10.9 per cent v/v in oxygen.[1] Raventos and Dee[4] stated the lower limit of inflammability to be as low as 5.2 per cent v/v in oxygen-nitrous oxide mixtures.

No reference has been made to the inflammability of the liquid in oxygen atmospheres similar to those encountered in the vaporizing chambers of the commonly used anaesthetic machines. As most of these vaporisers utilize the principle of saturating a fraction of the input gases with the vapour and subsequently diluting the mixture with by-passed gases, the lower limits of inflammability in oxygen, either as defined by Boivin[3] or by Raventos,[4] must be well below the concentration emerging from the vaporizing chambers; one must therefore assume that the risk of fire and explosion from electrostatic and other sources has not been eliminated.

There is no doubt that the liquid azeotrope in the prescribed proportions is non-flammable in air. Nevertheless, it is highly inflammable in oxygen and has already been responsible, in the experience of one of us (M.J.), for one minor conflagration which was extinguished with difficulty. If the fire hazard is to be avoided completely it will be necessary to use only air to vaporize the liquid, and this requires the use of non-return breathing equipment with assisted respiration. This method, besides being extravagant and perhaps wasteful, causes atmospheric contamination which theatre personnel often find objectionable. A modification of this method, combining low concentrations of the azeotrope in air with supplementation by intravenous agents, has been

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described,[5] and indicates that effective anaesthesia is no longer dependent on a constant supply of compressed gases; this system of anaesthetic management will be invaluable in circumstances where compressed oxygen is unavailable. There is no reason to doubt that halothane, administered in a somewhat similar but more convenient manner, should be equally, if not more, effective.[6]

Pharmacological investigations of the azeotrope were not reported before the appearance of the first clinical report.[1] It appears to have been assumed empirically that the accepted sympathomimetic action of ether should successfully antagonize the cardiovascular effects of halothane and thereby raise its margin of safety. It does not appear to have been considered that the effects of halothane on sympathetic activity may expose the true action of ether on the myocardium.

The successful use of the azeotrope in over 2,000 cases was described in this report, using various methods of administration which included the Boyle, Fluotec, and Heidbrink vaporizers in semi-closed and closed circuits with oxygen; the open mask drop was also used with continuous administration of oxygen by nasopharyngeal catheter. Respiratory depression and apnoea occurred with the closed and semiclosed methods and hypotension was encountered but was an inconstant finding.

Dobkin, Drummond, and Purkin[7] investigated the effects of the azeotrope on the circulatory dynamics and other functions of 50 patients. The method of anaesthesia consisted of pethidine-atropine premedication, induction with thiopentone-gallamine, and maintenance with nitrous oxide, oxygen, azeotrope 0.5 per cent to 1.0 per cent v/v with additional gallamine for relaxation; artificial ventilation was provided with an automatic ventilator and a non-rebreathing system was incorporated. They concluded that circulatory dynamics did not present the same problems as they had encountered with halothane, although some of their dogs anaesthetized with the mixture developed serious and sometimes fatal cardiac arrhythmias when adrenaline was injected intravenously.

In a second and more elaborate experimental study in dogs, Dobkin, Harland, and Fedoruk[8] compared the cardiovascular and respiratory effects of 2 per cent v/v halothane in oxygen with the azeotrope 3 per cent v/v in oxygen. They observed that the differences, though small, were statistically significant and concluded that they found the azeotrope easier to use than halothane. Their use of three references to substantiate the questioning of the report that halothane prevents surgical shock is misleading: two of the references are unrelated to shock and the third noted that although profound hypotension was observed during halothane, shock did not appear. If the suggestion that halothane prevents the appearance of shock and facilitates the resuscitation of shocked patients proves to be correct, there is no doubt that the drug can be regarded as having "distinctly individual features."[9]

Dechene and Hebert[10] reported the successful use of the azeotrope in a large number of pulmonary operations, using the azeotrope in low concentrations combined with nitrous oxide, oxygen, and suxamethonium. Wyant, Merriman, Harland, and Donaldson,[11] using higher doses of the mixture in a closed circuit

with oxygen, observed systolic pressures in volunteers as low as 42 mm. Hg with the cardiac output too low to be measured. The observations of the latter workers do not indicate that either prevents the cardiovascular and respiratory effects of halothane and it may, in fact, be adversely additive, as suggested by Raventos and Dee.[4]

Shortly after the appearance of the initial clinical report on the azeotrope we decided to compare its effects with those of halothane in a series of patients undergoing prolonged operations requiring general anaesthesia. Adult neurosurgical cases offered the best opportunities because our premedication was standardized to pethidine 50 mg. with atropine 0.6 mg., and induction and intubation were performed with thiopentone-suxamethonium. The proposed plan was to maintain anaesthesia with 10 L. per min. of a 50 per cent mixture of nitrous oxide and oxygen through a Fluotec vaporizer set at 2 per cent halothane. After approximately an hour on this mixture, the Fluotec was to be turned off and the gas mixture directed through an Azeotec, specially constructed for the purpose, set at 2 per cent. Non-rebreathing apparatus (Ruben valve) was to be used and the respiratory minute volume constantly measured with a Wright respirometer, respiration being assisted if the minute volume dropped below 6 L. per min. Systolic blood pressures were to be measured by sphygomanometry every few minutes and the pulse rate charted in the usual manner. The investigation came to an abrupt halt after the completion of the first case, details of which are as follows.

A thin female of 34 years of age had signs and symptoms of a tumour in the posterior cranial fossa, but was conscious, rational, and well nourished, with normal heart and lungs. Her blood pressure was 110/70. Premedication was pethidine 50 mg. and atropine 0.6 mg.; induction, thiopentone 200 mg. with suxamethonium 50 mg.; and maintenance, halothane 2 per cent with 10 L. per min. nitrous oxide and oxygen 50 per cent. Intravenous gluco-saline drip at 30 drops per min. was given and the operation was performed with the patient in the sitting position.

During the first hour of halothane-nitrous oxide anaesthesia the blood pressure remained steady at 75 mm. Hg systolic with adequate brain pulsation. The halothane was then stopped and the azeotrope 2 per cent introduced. A slowly progressive decline in blood pressure then commenced, without change in pulse rate, and after 20 min. reached the alarmingly low level of 30 mm. Hg systolic, the radial pulse being barely perceptible. Brain pulsation was no longer visible and a patchy cyanotic pallor appeared on the peripheral parts of the body, especially the fingers, hands, and forearms. Throughout the period of circulatory collapse respiration was deep and regular, of the hypoxic type, and the radial pulse was regular and very feeble at 90 beats per min.; neither assisted nor controlled respiration was required at any time. The azeotrope and nitrous oxide were immediately withdrawn and oxygen only administered for the next 3 min. during which time the normal pink colour of the skin gradually returned and pulsations became visible in the brain. Halothane 2 per cent in oxygen was then added and the blood pressure gradually returned during the next few minutes to 70 mm. Hg systolic. The halothane 2 per cent

in oxygen was continued for the next 2 hours and the operation successfully completed, the systolic pressure remaining about 75 mm. Hg. Consciousness returned approximately one hour postoperatively and, apart from some restlessness and confusion for the next twenty-four hours, recovery was uneventful.

For the next twelve months our interests were directed towards the development of a technique whereby surgical anaesthesia could be rapidly induced and maintained with halothane-oxygen only, all other agents, including preoperative sedatives, atropine, thiopentone, nitrous oxide, pethidine, relaxants, and vasopressors being eliminated. Early in the investigation it became obvious that deep surgical anaesthesia could not be induced expeditiously in all cases with 3 per cent halothane in the respiratory minute volume of oxygen. After careful trials we discovered that concentrations from 6-10 per cent of halothane in 5 L. of oxygen could be safely used for the induction of surgical anaesthesia of sufficient depth to permit easy intubation after 2-4 min.; thereafter any required depth of anaesthesia could be provided with smaller amounts of halothane. A specially adapted Fluotec was provided for this purpose and atropine was to a large extent eliminated because it was realized that it often caused undesirable distortion of the cardiovascular picture of halothane anaesthesia. Full details of this work are awaiting publication.

While the halothane-oxygen anaesthesia was being developed, we applied the procedure known as vasculometry and vasculography to help in assessing the effect of various drugs on the cardiovascular system. The apparatus consists of a small carbon microphone, energized by a 1½ volt dry battery, placed over the radial pulse or on the pulp end of a digit, and observing the pulsations on a small voltmeter, as described by Keating.[12] If the leads into the voltmeter are tapped in parallel and fed into an electrocardiograph, a pulse tracing is obtained on which change in amplitude, form, rate, and rhythm are clearly recorded: the latter adaptation has been reported by Lax, Feinberg, and Cohen[13] and called a vasculograph. A somewhat similar principle of monitoring the circulation has been applied by Schotz, Bloom, Helmsworth, Dodge, and Birkmire[14] who claim that the vasculogram is a reliable index of changes in the cardiac stroke volume output. It is beyond the scope of the present report to enter into a detailed discussion of the significance of vasculography in clinical practice, but we have accepted the precept that an increase in the amplitude of the peripheral pulse wave indicates either vasodilation or an increase in the cardiac output, according to the behaviour of the blood pressure. Similarly a decrease in the amplitude of the pulse wave means either vasoconstriction or a diminished cardiac output, again according to the behaviour of the blood pressure.[15, 16, 17] After considerable experience in the clinical use of vasculometry we agree with Schotz *et al.*[14] and Lax[13] that it, in conjunction with vasculography and sphygomanometry, represents a practical, convenient, and reliable means of monitoring the behaviour of the circulatory system in the anaesthetized patient.

Having achieved the aim of using halothane-oxygen only for all clinical investigations concerning halothane and at the same time having acquired

a reliable means for constantly recording the state of the circulation, particularly at very low pressures, we decided to look again at the azeotrope which was still attracting attention. We felt that the cardiovascular collapse encountered in our one case may have been coincidental to the use of the azeotrope and may perhaps have been more closely related to posture or to the nature of the operation.

Method

Elderly patients with normal cardiovascular and respiratory systems were selected. For the first few cases only those for cysto-diathermy were chosen as this procedure was usually sufficiently prolonged to permit a thorough investigation and seldom provokes the reflex circulatory effects of trauma. Subsequently, more major surgical operations were included and a total of twenty patients was investigated.

Premedication. Ten of the patients received no preoperative drugs of any kind. Each of the others received pethidine 50 mg. and promethazine 50 mg. two hours preoperatively.

Induction. Anaesthesia was induced in each patient with halothane 10 per cent in oxygen 5 L. per min. from a Fluotec (type mj) into a Waters' bag without the soda lime canister. There was spontaneous respiration. Anaesthesia of a depth sufficient to permit the insertion of a cuffed endotracheal tube was achieved in from 2-4 min.

Maintenance. After the insertion of the endotracheal tube halothane, 2-3 per cent in 10 L. per min. of oxygen into a Waters' bag with a non-return valve (Ruben) and a Wright respirometer incorporated was given. After 30 min., the Fluotec was turned off and the oxygen passed through an Azeotec set at 3 per cent, in accordance with Dobkin's experimental plan.[8]

Ventilation. Respiration was assisted gently by hand if the respiratory minute volume dropped below 10 L. per min. The precise effects of the azeotrope on respiratory activity were not measured. From the published reports it is obvious that it causes respiratory depression when administered in effective doses and it is impossible with any anaesthetic agent to achieve adequate surgical relaxation without causing some degree of depression. Although respiratory depression has little effect on oxygen uptake during halothane anaesthesia,[18] it limits the uptake of anaesthetic agent and output of CO_2, thereby introducing a variable which will affect the cardiovascular reactions: it was mainly to eliminate this variable that assisted respiration was used. Because of its extravagance this method is not recommended for routine clinical use, closed systems being preferable.

Monitoring. The systolic blood pressure (digital) was recorded at frequent intervals with a sphygmomanometer and vasculometer. Vasculograms were recorded before induction, immediately after the insertion of the endotracheal tube, after 30 min. of halothane anaesthesia, at frequent intervals during the administration of the azeotrope, and at 3-5 min. intervals after the withdrawal of the azeotrope and the re-introduction of halothane.

Results

From the surgical point of view there were no obvious differences between halothane and azeotrope anaesthesia. Muscular relaxation was adequate in all cases, which included a few lower abdominal laparotomies, and spontaneous respiration persisted with quiet and easy diaphragmatic respiration. Respiratory depression was moderate, transient, and easily controllable. The lungs remained easily inflatable and free from secretions. Bleeding from cut surfaces was minimal and sweating did not occur. The pupils remained constricted in all patients. The recovery of consciousness was always prompt and free from restlessness, delirium, and vomiting.

The cardiovascular reactions to the azeotrope, when administered in the above manner, were unlike those provoked by halothane and the pattern of change was remarkably constant. Halothane caused the usual hypotension coincident with vasodilatation, the hypotension being maximal during induction and settling at a higher level when surgical anaesthesia was established and the operation started. The pulse rate usually decreased slightly but remained within normal limits in all cases. The hypotension was invariably associated with a considerable increase, often five-fold, in the amplitude of the pulse wave with a deepening of the incisura and an increase in the amplitude of the dicrotic wave in those patients in whom the dicrotic wave was present before induction. The blood pressure and the amplitude of the pulse wave were unaffected by intermittent positive pressure inflation of the lungs and the duration of anaesthesia had little effect on them.

A further decline in the blood pressure followed the change to the azeotrope in twelve patients. The decline had usually started after 5 min. inhalation of the mixture and was slowly progressive during the experiment, the lowest level reached being 45 mm. Hg systolic after 25 min. of azeotrope anaesthesia. The rate of fall was accentuated by intermittent positive pressure inflation of the lungs, using pressures well within the normal range. In the remaining patients, the blood pressures were unaltered by the azeotrope. The azeotrope hypotension was associated with a patchy cyanotic pallor of dependent parts in six patients, clear evidence of circulatory stasis.

In all patients, including those with unaltered blood pressures, the azeotrope caused a progressive decrease in the amplitude of the pulse wave, an effect which was intensified by intermittent positive pressure inflation of the lungs. Blood pressure and pulse wave returned to their pre-azeotrope levels within a few minutes after the resumption of 2 per cent halothane anaesthesia.

After the complete elimination of the azeotrope a higher dose of halothane —6 per cent in oxygen 5 L. per min. with assisted respiration—was given to three patients to reproduce a hypotension of similar degree to that encountered during the administration of the azeotrope, in each case 50 mm. Hg systolic. In each instance the pulse wave during halothane hypotension was considerably higher than the wave associated with the azeotrope; the typical sequence of change in the pulse wave and blood pressure is illustrated in Figure 1.

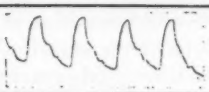
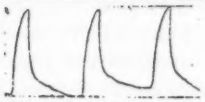
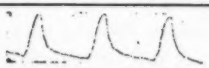
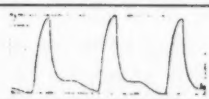
ANAESTHETIC AGENT	TIME (mins)	PULSE WAVE recorder sensitivity 1mv/1cm.	SYSTOLIC PRESSURE mm. Hg.
Before induction	0		130
FLUOTHANE 10%	4		70
FLUOTHANE 2%	30		78
AZEOTROPE 3%	37		50
FLUOTHANE 2%	44		70
FLUOTHANE 6%	49		50
FLUOTHANE 1%	63		85

FIGURE 1. Vasculography during anaesthesia in a male of 63 years undergoing suprapubic prostatectomy. Heart and lungs are normal; blood pressure 130/90. No premedication was given. Anaesthesia was induced and maintained with halothane-oxygen; azeotrope was added after thirty minutes. Note the considerable fall in the amplitude of the pulse wave and in the systolic pressure. The induction of a similar degree of hypotension, 50 mm. Hg systolic, with a high dose of halothane at 49 minutes was not associated with a significant decrease in the amplitude of the pulse wave. The final tracing was obtained as the operation was finishing.

DISCUSSION

The empirical assumption that ether may antagonize the circulatory effects of halothane may be correct when low and ineffective doses of the drugs are used. In these circumstances, the dose of halothane is too small to have any significant influence on autonomic activity and the even lower dose of ether will probably not impair circulatory dynamics, although, when clinically effective doses of the azeotrope are administered, it is evident that the ether

fraction rapidly induces signs of acute circulatory failure in a large proportion of patients already satisfactorily anaesthetized with halothane.

To obtain this reaction to ether it may seem that we have used unnecessarily large doses of halothane, the administration of halothane 10 per cent in oxygen being contrary to previous recommendations.[19] In developing this apparently high-dose technique we were interested primarily in finding a practical and safe procedure for the induction and maintenance of anaesthesia, applicable in all clinical circumstances and independent of clumsy equipment; we were also interested in defining the capabilities of halothane when used as a sole agent for all types of surgical operations. In the course of our investigations it became obvious that it was difficult to induce a reasonable depth of surgical anaesthesia with halothane 2 per cent in oxygen, although this dose was effective when combined with nitrous oxide: several of the more robust patients were still objecting after inhaling 2 per cent halothane in oxygen for 20 minutes. The dose was gradually increased and eventually the 6-10 per cent range was adopted for the induction of anaesthesia. Satisfactory results have now been obtained in many hundreds of patients and the procedure has been subjected to special investigations relating to cardiovascular and respiratory reactions, details of which will be published elsewhere.

Many patients, on recovering consciousness after the induction of anaesthesia with halothane 10 per cent in oxygen, have no unpleasant recollections and several were unable to recall any smell or other subjective experience. Attempts to achieve this type of induction with the azeotrope 10 per cent in oxygen had to be abandoned as several patients objected violently to the intolerable pungency of the ether fraction. The addition of ether to halothane for the purpose of inducing anaesthesia can therefore be regarded as highly objectionable and possibly dangerous because of the explosion hazard when effective concentrations of the mixture are mixed with oxygen. It was therefore impossible to conduct a truly comparative study of halothane and its ether azeotrope. It is not improbable, however, that the halothane-azeotrope sequence which we adopted for our investigation produced cardiovascular reactions similar to those induced by the azeotrope used alone: the circulatory collapses observed by us appear very similar to those described by Wyant *et al*,[11] using the azeotrope in a closed circuit.

It would appear that the introduction of the azeotrope into clinical practice was at least premature. The cause and significance of the cardiovascular reaction to halothane are not yet fully appreciated and it would be most unwise to assume that they are detrimental to the patient. Any attempt to influence them, particularly by the use of agents known to be myocardial depressants, may do more harm than good. We now have reliable evidence indicating that halothane causes depression of sympathetic activity and its haemodynamic actions can be correlated, at least in part, to its effects on autonomic nervous activity.[9, 20, 21, 22] It is fully recognized that the administration of surgically ineffective doses of ether in the presence of sympathetic blockade at any level causes a rapidly progressive circulatory failure, survival from its toxic effect being dependent on an intact sympathetic nervous system.[23]

The sequence of events which we have observed following the administration of ether to patients anaesthetized with halothane has a striking similarity to that described by Brewster, Isaacs, and Andersen[23] in dogs following the inhalation of ether after sympathetic blocks had been induced at various levels. It can therefore be concluded that there are neither physical nor pharmacological grounds to justify the administration of mixtures of ether and halothane to patients. Intensive clinical experience in many parts of the world has indicated that halothane by itself is perfectly capable of providing safe, efficient, and easily reversible anaesthesia without sequelae of any kind when administered in a competent manner. It is not improbable, however, that its unique pharmacological properties may profoundly alter the pharmacological actions of other drugs.

Summary

1. The halothane-ether azeotrope 3 per cent in oxygen has been administered to twenty patients already adequately anaesthetized with halothane. Respiration was artificially maintained between 8-10 L. per min., using non-return breathing equipment.

2. Systolic blood pressures were frequently recorded by sphygmomanometry and vasculometry. The amplitude of the peripheral pulse was continuously displayed by a simple vasculometer and vasculograms were obtained at frequent intervals.

3. It was observed that the azeotrope in most patients caused a progressive decline in blood pressure which reached profound levels in five patients. The hypotension was associated with a decrease in the amplitude of the pulse wave in all cases and circulatory stasis with cyanosis was seen in six cases.

4. It is concluded that the administration of mixtures of ether and halothane is illogical and the physical and pharmacological reasons for this conclusion are presented.

5. It is suggested that halothane by itself in oxygen is fully capable of providing all the necessities of safe and effective anaesthesia.

Acknowledgments

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Résumé

On est d'accord actuellement que, dans l'air, le mélange azéotrope halothane-éther n'est pas inflammable. Dans les mélanges de protoxide et d'oxygène, la limite inférieure d'inflammabilité est 5.2% v/v, concentration qui est de beaucoup inférieure à ce qui sort des endroits d'évaporation de la plupart des

vaporisateurs d'usage courant qui réalisent l'application du principe de saturer une partie du débit gazeux et ensuite de diluer ce gaz saturé avec du gaz qui arrive dans le circuit en évitant le vaporisateur. Si l'on emploie le mélange azéotrope pour renforcer l'anesthésie protoxide-oxygène, il faudra, en conséquence, présumer que les risques d'explosion par l'électricité statique et les autres sources ne sont pas éliminés.

Au cours des douze derniers mois, nous avons fait des recherches qui nous permettent d'affirmer qu'il faut 6 à 10% d'halothane avec de l'oxygène pour induire une anesthésie en toute sécurité et dans un délai raisonnable chez des malades non atropinés. C'est une technique qui nous a donné d'excellents résultats chez plusieurs centaines de malades et nous a fourni une anesthésie assez profonde pour nous permettre d'intuber au bout de deux à quatre minutes tous les types de malades. Au retour à la conscience, la plupart des malades ne se souviennent d'aucune odeau désagréable ni d'autre expérience subjective à part la perte soudaine de conscience. A la suite de l'induction de l'anesthésie avec cette concentration d'halothane dans l'oxygène, il est possible de maintenir une anesthésie chirurgicale profonde durant de longues intervalles avec de 4 à 7% d'halothane dilué dans seulement 250 à 500 ml. d'oxygène à la minute introduits dans un circuit fermé et avec respiration contrôlée. Des détails complets des aspects académiques et pratiques de cette méthode d'anesthésie sont en préparation pour publication. Nous avons dû abandonner nos tentatives de faire la même chose avec le mélange azéotrope parce que les malades se sont objectés violemment à l'odeur repoussante de la portion d'éther.

On a pensé que l'éther devrait contrebalancer les effets cardiovasculaires de l'halothane. On n'a pas songé à la possibilité que l'halothane puisse potentialiser l'action cardiotoxique de l'éther. Cette dernière possibilité est toutefois d'extrême importance parce qu'il est connu que la survie à la suite de l'éther n'a lieu que si le système sympathique est intact et, par ailleurs, nous savons que la réponse cardiovasculaire à l'halothane, pour une partie du moins, est attribuable à la dépression de l'activité sympathique.

Pour en venir à préciser si l'halothane augmente les dangers de l'éther, les auteurs ont administré le mélange azéotrope 3% avec de l'oxygène à une série de vingt vieillards déjà anesthésiés adéquatement avec l'halothane oxygène. Nous avons employé une méthode de recherche non utilisée antérieurement en anesthésie clinique, elle consiste en vasculométrie, vasculographie et sphygmomanométrie dont nous publierons les détails ailleurs. Nous avons observé que le mélange azéotrope a souvent causé un collapsus circulatoire profond en quelques minutes après son addition. L'élimination de l'éther et l'installation de nouveau de l'halothane à 2% avec de l'oxygène ont été suivies, dans tous les cas, de la disparition du collapsus circulatoire et nous avons conclu, en conséquence, que l'halothane sensibilisait dangereusement les malades aux effets cardiotoxiques de l'éther.

REFERENCES

1. Hudon, F., Jacques, A., & Boivin, P. A. Fluothane-Ether: An Azeotropic Mixture. Canad. Anaesth. Soc. J. *5*: 403 (1958).

2. LOTT, W. A. Medicinal Chemistry as a Basic Science in Anesthesiology. Anesth. & Analg. *38*: 461 (1959).
3. BOIVIN, P. A., HUDON, F., & JACQUES, A. Properties of the Fluothane-Ether Anaesthetic. Canad. Anaesth. Soc. J. *5*: 409 (1958).
4. RAVENTOS, J., & DEE, J. The Action of the Halothane-Diethyl Ether Azeotropic Mixture on Experimental Animals. Brit. J. Anaesth. *31*: 46 (1959).
5. ADAMS, A. K., LAMBRECHTS, W., & PARKHOUSE, J. Clinical Trial of an Azeotropic Mixture. Acta. Anaes. Scand. *3*: 189 (1959).
6. WOODS, M. A., & BROWN, T. A. A Marrett Draw-Over Inhaler Modified for Halothane. Brit. J. Anaesth. *31*: 321 (1959).
7. DOBKIN, A. B., DRUMMOND, K., & PURKIN, N. Anaesthesia with the Azeotropic Mixture of Halothane and Diethyl Ether. Brit. J. Anaesth. *31*: 321 (1959).
8. DOBKIN, A. B., HARLAND, J. H., & FEDORUK, S. Comparison of the Cardiovascular Effects of Halothane and the Halothane-Diethyl Ether Azeotrope in Dogs. Anesthesiology *21*: 13 (1960).
9. PATON, W. D. M. Halothane and Autonomic Nervous Activity. Lancet *ii*: 554 (1959).
10. DECHENE, J. P., & HEBERT, C. Fluothane-ether Anaesthesia for Pulmonary Surgery. Canad. Anaesth. Soc. J. *7*: 100 (1960).
11. WYANT, G. W.; MERRIMAN, J. E.; HARLAND, J. H.; & DONALDSON, H. V. The Cardiovascular Effects of the Azeotropic Halothane-Ether. Canad. Anaesth. Soc. J. *7*: 91 (1960).
12. KEATING, V. J. A Simple Pulse Indicator. Brit. Med. J. *i*: 1188 (1952).
13. LAX, H., FEINBERG, A. W., & COHEN, B. M. Studies of the Peripheral Pulse Wave. J. Chron. Dis. *3*: 618 (1956).
14. SCHOTZ, S.; BLOOM, S. S.; HELMSWORTH, F. W.; DODGE, H. C.; & BIRKMIRE, E. L. The Ear Oximeter as a Circulatory Monitor. The I.R. Pulse: A Moment to Moment Guide to Cardiac Output. Brit. J. Anaesth. *31*: 190 (1959).
15. WRIGHT, S. Applied Physiology. London: Oxford University Press (1940).
16. WIGGERS, C. J. The Pressure Pulses in the Cardiovascular System. London and New York: Longmans, Green and Co. (1928).
17. WIGGERS, C. J. Reminiscences and Adventures in Circulation Research. New York and London: Grune and Stratton (1958).
18. JOHNSTONE, M. Collapse after Halothane. Anaesthesia *14*: 410 (1959).
19. JOHNSTONE, M. The Human Cardiovascular Response to Fluothane. Brit. J. Anaesth. *28*: 392 (1956).
20. RAVENTOS, J. The Action of Fluothane — a New Volatile Anaesthetic. Brit. J. Pharmacol. *11*: 394 (1956).
21. PRICE, H. L.; LINDE, H. W.; JONES, R. E.; BLACK, G. W.; & PRICE, M. L. Sympatho-Adrenal Responses to General Anaesthesia in Man and their Relation to Haemodynamics. Anesthesiology *20*: 563 (1959).
22. THROWER, W. B.; DARBY, T. D.; ALDINGER, E. E.; & SPROUX, J. H. Effects of Halothane Anaesthesia on the Ventricular Contractile Force in the Human and in the Dog. Fed. Proc. *19*: 274 (1960).
23. BREWSTER, W. R., ISAACS, J. P., & ANDERSON, T. W. The Effects of Ether on the Myocardium of the Dog and its Modification by the Reflex Release of Epinephrine and Nor-Epinephrine. Am. J. Physiol. *175*: 399 (1953).

CARDIAC ARREST: A REPORT ON TEN CASES*

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THIS IS a presentation of some cases of cardiac arrest which recovered from the event. It is hoped that these will be of interest and possibly of some use in helping to forcast the outcome of some of the more serious cases. Ten cases are offered, all of which recovered to the extent that they would appear to be able to live a normal life in the future.

The first case illustrates how even in frankly adverse conditions a good result can be obtained.

Case 1: Attempted Bronchogram under Local Anaesthesia

This procedure was being performed on an 18-year-old woman in the X-ray Department by a surgeon using topical hexylcaine as the anaesthetic agent. A small but unknown amount of this agent had just been sprayed into the trachea when the patient started to convulse. The surgeon immediately sent for an anaesthetist and by the time one arrived the patient was black with cyanosis. Some further delay was occasioned in getting the anaesthetic machine going.

It proved impossible to ventilate the patient using the bag and mask because of pharyngeal obstruction from grossly enlarged tonsils. Thiopentone (50 mg. i.v.) was given, in order to control the convulsions, and an attempt was made to intubate the patient. Intubation was greatly hindered by the huge tonsils and the presence of fluid in the pharynx. While this was being completed the patient was observed to go into cardiac arrest. The surgeon asked for a scalpel, which was promptly produced, albeit from another room. Thoracotomy followed by cardiac massage was successful in quickly restarting the heart. Meanwhile the patient was ventilated with oxygen through the endotracheal tube. In due course the chest was closed in the normal manner.

Treatment. This patient was not in arrest long, perhaps little over a minute before massage was begun, but she suffered severe hypoxia for several minutes prior to that; however, an EEG taken within 15 minutes showed a waking pattern. It was therefore felt that there was little to worry about from a neurological point of view and this was subsequently shown to be the case. Within 2 hours of her cardiac arrest she was awake and talking. She had a stormy convalescence due to infection of her thoracotomy wound, but as far as could be ascertained she was mentally normal on discharge.

Case 2: Change of Dressings to Third Degree Burns

A 15-year-old boy weighing 130 lb., had a marked toxaemia from extensive burns covering the posterior aspect of his trunk and upper limbs. His haemo-

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globin was 69 per cent, and his general condition was only "fair." His premedication (meperidine 50 mg. and atropine 0.3 mg. given 45 minutes before operation) did not sedate him, and he arrived in the operating room very frightened.

He was anaesthetized on his bed, because of pain, through a cut-down intravenous catheter in his leg, using thiopentone, 150 mg. followed by succinylcholine 40 mg. and decamethonium 2 mg. After ventilation with oxygen an attempt was made to spray his trachea with lidocaine, but this was found to be impossible owing to the awkward angle (on a ward bed), and was immediately abandoned. He was then without further ventilation intubated without difficulty. His colour was good until immediately, on intubation, he lost all colour and pulse. Cardiac arrest was apparent and the surgical resident immediately opened the chest and massaged the heart, which recommenced a normal rhythm very rapidly. Duration of arrest was again of the order of 1 minute.

This case was difficult to explain at the time, but it would appear to be very similar to a case reported by Hueston Villiere and Flemming of Melbourne, Australia.[1] They also quote a similar case reported by Finer and Nylen of Sweden. A similar but fatal case occurred at another local hospital, and it might be that reflexes in these cases are unduly sensitive to intubation.

Treatment. This patient's general condition was treated with 1,000 c.c. of blood in the operating room and serum albumen 50 c.c. prophylactically for cerebral oedema. Atropine and methedrine were given intravenously at the time of massage. He was irrational for 6 hours and then responded. In the evening his temperature was 102° and he was actively cooled with fans and ice packs. On the following day he seemed mentally satisfactory, apart from being a little disorientated as to time. Two days later he was entirely normal.

These two patients were only in arrest for approximately 1 minute, but the second, owing perhaps to his poorer general condition with toxaemia and anaemia, showed some signs of cerebral damage. Both these patients had their chests opened, and this is essential if there is to be hope of success.

Case 3

Preoperative condition. A 75-year-old man was suffering from acute cholecystitis complicated by known arteriosclerotic heart disease with a complete heart block, the apex rate was 40 per minute.

The premedication was meperidine 50 mg. and atropine 0.6 mg. given one hour before operation. Induction was with thiopentone 0.25 gm. followed by succinylcholine 40 mg. for intubation. Ether, nitrous oxide, and oxygen were used for maintenance. During exploration of the gall bladder bed, 34 minutes after the commencement of the anaesthetic, cardiac arrest occurred. Massage was attempted through the abdomen in this case, for obvious reasons, but quickly abandoned and a separate incision made in the thorax. The patient responded fairly rapidly to cardiac massage, recommencing his normal slow rhythm. Total time of his period of arrest was 2 minutes. He had no postoperative troubles referrable to his arrest, despite his shaky cardiovascular system, and toxaemia from his cholecystitis.

Case 4

A 20-year-old woman had an open heart operation. In the immediate post-operative period she developed a cardiac tamponade and while being prepared for a thoracotomy had cardiac arrest. Cardiac massage was undertaken rapidly with a good result, and she regained consciousness on the operating room table where she could see the clock and exclaimed about the time. She presumably had amnesia for the period intervening between the two operations.

Case 5

After an open heart operation on a male patient cardiac arrest occurred in the recovery room owing to irritable conduction tissue, conveniently before the eyes of the surgeon. Arrest occurred again in the operating room while the bleeding points were being tied off. On this second occasion the heart would not restart until after a rapid blood transfusion had been given, despite adequate massage as demonstrated in the electroencephalogram tracing shown in the accompanying figure.

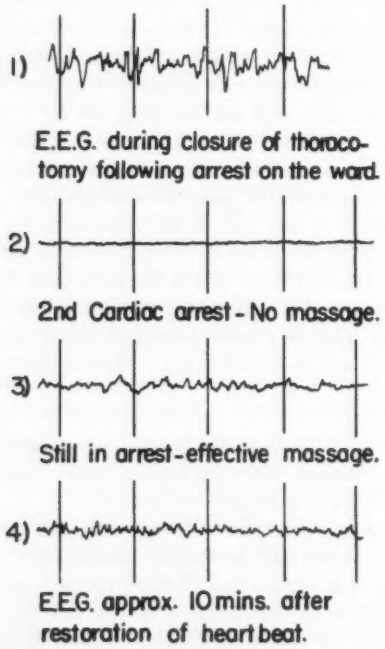

FIGURE 1. An EEG of case 5.

The electroencephalogram shows that cardiac massage was very effective. The EEG was also satisfactory only 10 minutes after restoration of normal rhythm. It was therefore predicted that the neurological outcome would be satisfactory—which indeed it was.

Case 6

A child had a cardiac arrest on the table, and effective massage was rapidly performed. He regained consciousness on leaving the operating room, and was calling loudly for his mother within seconds.

Case 7

A male patient was being cooled preparatory to craniotomy under hypothermia. On being lifted from the ice bath he developed ventricular fibrillation which required 20 minutes of massage before regular rhythm could be regained. He appeared to have suffered no ill effects from this episode. Undoubtedly the cooling helped here to give some protection.

Case 8

Cardiac arrest occurred in a 6-year-old child on introduction of an oesophageal temperature probe. Normal rhythm was established within 1 minute, and convalescence was uneventful from the neurological point of view.

In these eight cases cerebral circulation was interrupted for a brief period only, and from the neurological point of view gave little cause for concern. In each of these cases the cause of arrest was reversible, being reflex, conduction interference, bleeding, or hypoxia.

What then about the longer cases of arrest? Occasionally one "gets away" with a longer period of time than three or four minutes, but usually this is not the case. Corday Eliot and Cole Seymour,[2] in analysing the results of over 100 cases of cardiac arrest found only 2 patients out of 30 who had survived when treatment had been delayed for over 4 minutes, and both of these survivors had permanent brain damage. In contrast, in 78 cases where treatment was started within the 4-minute period, 33 made a complete recovery, while those that did not had a major complicating factor present, such as diminished pulmonary function or hypovolaemia. Despite this, it is certainly well worth while to treat the prolonged arrest aggressively, as an unexpectedly good result sometimes occurs, especially in children. The following case is an example of such a result.

Case 9: Intended Operation—Tonsillectomy and Adenoidectomy

The patient, a 5-year-old boy, was given premedication of meperidine 50 mg. and atropine 0.3 mg. 45 minutes preoperatively; induction of thiopentone 150 mg., succinylcholine Cl. 40 mg., intubated; and maintenance of ether, nitrous oxide, and oxygen. The arrest occurred about 10 minutes after induction and about 5 minutes after the commencement of the ether. It was only discovered when the anaesthetist noticed the patient's colour.

The duration of arrest was unknown but guessed at being at least 3-4 minutes. Following cardiac massage and return of spontaneous rhythm his EEG was flat for 2 hours. The patient was given 50 c.c. of serum albumen intravenously and his temperature was kept in the lower normal range with chlorpromazine and sedation, ice, and fans. On the second and third day his decerebrate rigidity eased and he became semi-conscious. On the fourth day he spoke and then

made a fairly rapid recovery. At the end of the first month he could walk fairly well, and by two months he appeared to be normal in every respect. This boy is now in his third year at school and he has not failed a grade. His school report cards show high grades and he plays games and sports with the other boys quite normally. His parents are quite happy with his progress.

The recuperative powers of children from this sort of disaster would appear to be quite remarkable. This is also shown by the following much more severe case.

Case 10

An infant, aged 6 months, was operated on for a patent ductus under ether anaesthesia. During the entire procedure the child was cyanosed owing to chronic infection and bronchospasm. At the end of the procedure the left lung was collapsed and uninflatable. Cardiac arrest was treated by immediate massage, the thorax being still open. The infant required bronchoscopy and forceful re-inflation of the lung. Spontaneous rhythm did not return for 8 minutes. Oxygenation was inadequate throughout because of bronchospasm.

Postoperatively the EEG was flat and there was no response to stimuli: convulsions were prominent and controlled with phenobarbitone. For two weeks the patient did not move all her limbs and her plantar responses did not return to normal. The head was still held hyperextended. At four weeks she was not appreciably changed; she turned towards noise but appeared quite definitely blind. She was seen one month ago and appears to be a bright child of two years of age and the neurologist states that she would appear to be normal. She has however a strabismus which may or may not have some connection with the arrest.

These last two cases demonstrate the more severe problems presented by prolonged cardiac arrest. What then of the treatment? In our experience if the patient is well ventilated and adequately transfused, rapid restoration of spontaneous rhythm occurs. As Gain[3] and others have pointed out, the electroencephalogram is extremely valuable as a monitor of the state of the cerebral circulation, particularly in cardiac and certain other poor risk cases. It is also useful in prognosis following cardiac arrest, as shown by Bellville and Howland.[4]

As a rough guide it may be stated that the prognosis is good if the fast activity in the EEG is restored within 1 hour. If it continues flat for over 4 hours there is strong evidence of irreversible cortical damage.

Conclusion

Our experience confirms that of many others that, provided everybody is well rehearsed, a good result can often be obtained provided cardiac arrest is quickly spotted and treated. However if the prearrest period is complicated by respiratory, cardiovascular, or other factors, such as toxaemia, the final outcome may be seriously jeopardized. The remarkable recuperative powers of children, as shown in the last two cases, should be born in mind when treating these serious problems.

Summary

Ten cases of cardiac arrest who recovered from the event are presented. The last two cases show the remarkable powers of recuperation possessed by children in recovering from what appeared at the time to have been a very severe degree of brain damage.

REFERENCES

1. Fleming, W. B.; Hueston, J. T.; Stubbe, J. L.; & Villiers, J. D. Two Episodes of Cardiac Arrest. Brit. Med. J. *i*: 157 (1960).
2. Cole, S. L., & Corday, E. The Internist and Cardiac Arrest. A.M.A. Arch. Int. Med. *104*: 37 (1959).
3. Gain, E. A. The Practical Value of the Electroencephalogram during Anaesthesia. Canad. Anaesth. Soc. J. *6*: 227 (1959).
4. Bellville, J. W., & Howland, W. S. Prognosis after Severe Hypoxia in Man. Anesthesiology *18*: 389 (1957).

MANNED SPACE EXPLORATION AND THE POSSIBILITY OF HYPOXIA*

R. H. LOWRY, M.D.†

THE IMMINENCE of manned space flight permeates the thinking of the world today. The flight of manned satellites is no longer a fantastic dream of the distant future, for the impending orbiting of such vehicles will herald man's first faltering footsteps into the unknown vast depths of space.

Engineering technology, combining the specialties of aerodynamics, structures, propulsion, communications, and many other facets, has proved the feasibility of vehicular space travel. The critical design of such vehicles demands the detailed evaluation of engineering systems for reliability, ease of maintenance, and general performance under the stress of space flight. Moreover, practical engineering design, manufacture, and test must be backed up by many man years of fundamental research in various fields such as chemistry, metallurgy, and geophysics. The rapid expansion of engineering technology has provided theoretical knowledge and facts so that men are capable of producing the vehicles which are propelled out of this world to the abyss of space. The early unmanned vehicles have been fabricated and flown, but we must remember that today we are interested in manned space flight and exploration. Such an interest imposes many detailed problems which must be surmounted in our planned program for space flight. Unfortunately, our medical knowledge of this strange material called man is somewhat lacking in many facets so important in space flight. The engineer is dealing with materials and structures which have a specific yield point at some given stress. However, the aerospace medical group is responsible for the well-being of man in flight. Man, however, is a mixture of organic and inorganic substances with a mental component which decrees a rather wide variation in the ability of the various individuals to cope with combined stresses. This interphase of medicine and engineering presents a fertile area to apply the general biological sciences for the optimum integration and most efficient use of humans in the manned machine concept associated with this bold venture into space.

The very basis of space medicine, of course, is sound clinical medicine. However, when we apply this field of medicine to man in flight, we rapidly become involved in such problems as protective clothing against hostile environments, in-flight feeding, sealed cabins with associated problems of gaseous exchange, waste disposal, toxicity, and so on. Furthermore, the selection of

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crews, including their physiological training, their survival training, the associated problems of corpuscular and electromagnetic radiation, weightlessness, remoteness, the possibility of failure of the cabin pressurization system resulting in a rapid decompression, and many other problems requires continual surveillance of the medical aspects associated with such manned flight.

An essential aspect of man's environment, whether he is on the ground or in a vehicle in flight, is his oxygen requirements. A momentary review of our basic sciences will remind us that the essential aspect of oxygen concentration as far as man is concerned is the partial pressure of the gas which reaches the alveoli. Likewise, we will remember that as the altitude increases, the partial pressure of the oxygen decreases, even though the percentage by volume of the oxygen in the environment remains constant up to many thousand feet. It is this decreasing partial pressure of oxygen as the altitude increases that causes the respiratory difficulty to our flyer. A moment's further reflection will remind us of the oxygen dissociation curves for human blood. Oxygen combines reversibly with haemoglobin in a unique manner to form oxyhaemoglobin. Three points are paramount regarding this curve. (1) The combination of haemoglobin with oxygen is influenced by the partial pressure of the oxygen in the surrounding medium. This, of course, has a direct effect on the ability of the blood to transport oxygen to the tissues of the body at various altitudes. (2) Haemoglobin has a relatively high affinity for oxygen at certain high partial pressures of oxygen, and a relatively low affinity for oxygen at lower pressures. This, of course, forms the S-shaped curve with which you are all familiar in the oxygen dissociation graph. The practical application of such a curve is that blood has a high capacity for oxygen at the partial pressure of oxygen in the lungs when the oxygen partial pressure is relatively high, and a low capacity at the lower partial pressure of oxygen which is found in the tissues. This results in a rapid loading of oxygen in the lungs and a rapid unloading of oxygen in the tissues. (3) The third point to remember from the dissociation curve is the shift of the curve to the right or to the left, depending on the variation of the pH of the blood. Therefore, as the pH of the blood becomes more alkaline, the oxygen capacity of the haemoglobin is increased; and as the blood becomes more acidic, the percentage of oxygen saturation of the haemoglobin is decreased. As the human ascends, an appreciable hypoxia associated with approximately 84 per cent oxyhaemoglobin saturation occurs, on the average, at about 13,000 feet while breathing normal air. A serious handicap is noticeable around 17,000 feet, with imminent collapse, on the average, at approximately 19,000-20,000 feet. When breathing pure oxygen, however, the altitudes are increased, so that utilizing pressure breathing the appreciable hypoxia is first noted around 42,000 feet, with serious handicap and probably imminent collapse occurring around 44,000 or 45,000 feet altitude.

When discussing space flight, we must remember that for all intents and purposes our vehicle is operating in a vacuum. It is most essential, therefore, that the astronaut be protected by being enclosed in an environment that is capable of sustaining life and also permitting him to efficiently carry out his

expected work load. Protection for man in space flight will, therefore, require what is known as a sealed cabin. This sealed cabin must maintain an artificial atmosphere closely monitored with rigid parameters.

Let us examine some of the primary requirements of the human body that must be considered when designing the sealed cabin of a manned space vehicle. To maintain man's mental acuity, a partial pressure of oxygen approximately equal to that found at sea level, or 160 mm. Hg, will be required. The internal cabin pressure should be maintained below 18,000-20,000 feet, or an equivalent of 350 mm. Hg, in order to insure that the ambient pressure will prevent bends, chokes, and so on from developing in the astronaut during flight. The difference between the partial pressure of oxygen in the cabin and the total cabin partial pressure must be made up with nitrogen or some other inert gas in order to insure that there is no oxygen toxicity, respiratory pathology, or problem of flammability with which the astronaut will have to cope. Oxygen toxicity develops when the human is subjected to a partial pressure of oxygen of 425 mm. or more for a moderate length of time. The fact that tolerance to oxygen is limited only if its partial pressure exceeds about 425 mm. Hg would indicate that pure oxygen can be breathed with impunity at all altitudes above 15,000 feet where the partial pressure of the environment equals around 425 mm. Hg. Herein, however, a man may encounter further difficulties if a blockage of one of the alveolar ducts of the lung occurs owing to a mucous plug or some other obstruction developing. If an astronaut is breathing pure oxygen, he would, therefore, have partial pressure resulting from only a mixture of oxygen, carbon dioxide, and water vapour in his alveolar sacs without the partial pressure of an inert gas such as nitrogen. There is then the possibility of having the oxygen absorbed through the alveolar walls with the resultant collapse of part of the lung due to the lack of partial pressure from an inert gas, such as nitrogen, remaining in the lungs and keeping them inflated.

A most important point in the operation of a sealed cabin is the adequate removal of carbon dioxide and other toxic gases from the recycled air. Carbon dioxide in a sealed cabin environment is harmful to a man when continuously present in excess of 3 per cent of the total atmospheric gas, and preferably should be maintained below a concentration of 0.5 per cent. The levels of oxygen and carbon dioxide in the environment, therefore, must be adequately monitored at all times in order to maintain man's efficiency. It must also be remembered that organic and inorganic contaminants may be given off in the form of gases or vapours from the use of paints, resins, refrigerants, carbon monoxide due to smoking, human wastes, and so on, in such a sealed cabin. Such toxic compounds, even though in minute quantities, must be meticulously removed from the breathed environment during the recycling process in order to insure that acute or even chronic toxic effects will not hamper the operation of the central nervous system of the astronaut.

In addition to supplying an adequate gaseous environment in the cabin, the temperature and humidity must be controlled for the comfort and, indeed, the very existence of the human organism. While one could state many cases where hypoxia had been the dominant factor in an emergency during terrestrial

flight, it must be pointed out that the humidity of the atmosphere is also of utmost importance in the sealed cabin environment in order to control the fluid balance and the temperature of the body. A change in the fluid balance of the body can readily affect the acid-base balance of the blood, therefore directly affecting the pulmonary ventilation with possible serious physiological effects on the space crewman.

For short space flights, where weight is not an insurmountable obstacle, the utilization of cryogenic systems will permit a balanced atmosphere to be maintained in the cabin in an open-ended system. However, for longer flights of several weeks duration, chemical-oxygen regeneration systems utilizing hydrogen peroxide or potassium superoxide will be required to produce sufficient oxygen while maintaining a satisfactory O_2 production/weight ratio for efficient operation. CO_2 and other toxins will be absorbed chemically or regenerated to O_2. Travel involving several months or more duration in space vehicles will require photosynthetic gas exchangers involving a combination of algae and broad leaf plants for the conversion of CO_2 to O_2 and food for use in flight. The regeneration of water in such systems will be required for space flight operations of approximately three weeks or more, whereas the regeneration of food becomes an efficient operation in flights involving approximately three months duration or more.

The reliability of present-day sealed cabins suggests the requirement for the astronaut to wear a full pressure suit for physiological protection in the event of the loss of cabin pressure in a rapid decompression in the cabin. The wearing of such safety equipment brings forth other problems even when it is not inflated, for the garment is heavy and warm and interferes to some extent with the comfort, mobility, and the normal evaporation of perspiration and, hence, the cooling of the man. It is essential, therefore, that adequate ventilation be maintained at all times through the suit to maintain the normal body temperature of the crewman in such an environment.

Space exploration in its true sense will require the landing of vehicles on other planets. After a landing, the aircrew will leave the protective environment of their sealed cabins and explore the surrounding planets. In accordance with our best knowledge at the present time, it will be necessary for such explorers to wear constantly adequate full pressure suit clothing which not only gives a protective ambient pressure around the body, but on leaving the spacecraft must include such things as radiation protection, communication, and mobile environmental recycling apparatus to absorb CO_2 and other toxic gases and provide fresh oxygen continually for man's use. In such instances hypoxia or lack of oxygen could result from yet another aspect, namely, the effect of radiation on any bottled gas being carried in the mobile pack; for pressurized oxygen subjected to intense radiation has the possibility of producing ozone which, of course, is highly toxic to humans.

Hypoxia, or lack of adequate oxygenation, has been discussed in its broadest aspect as a problem in the space cabin environment arising as a result of many factors that might occur during flight, rather in detail on the technical aspects of pure hypoxia due to oxygen lack *per se*. Associated problems of manned space

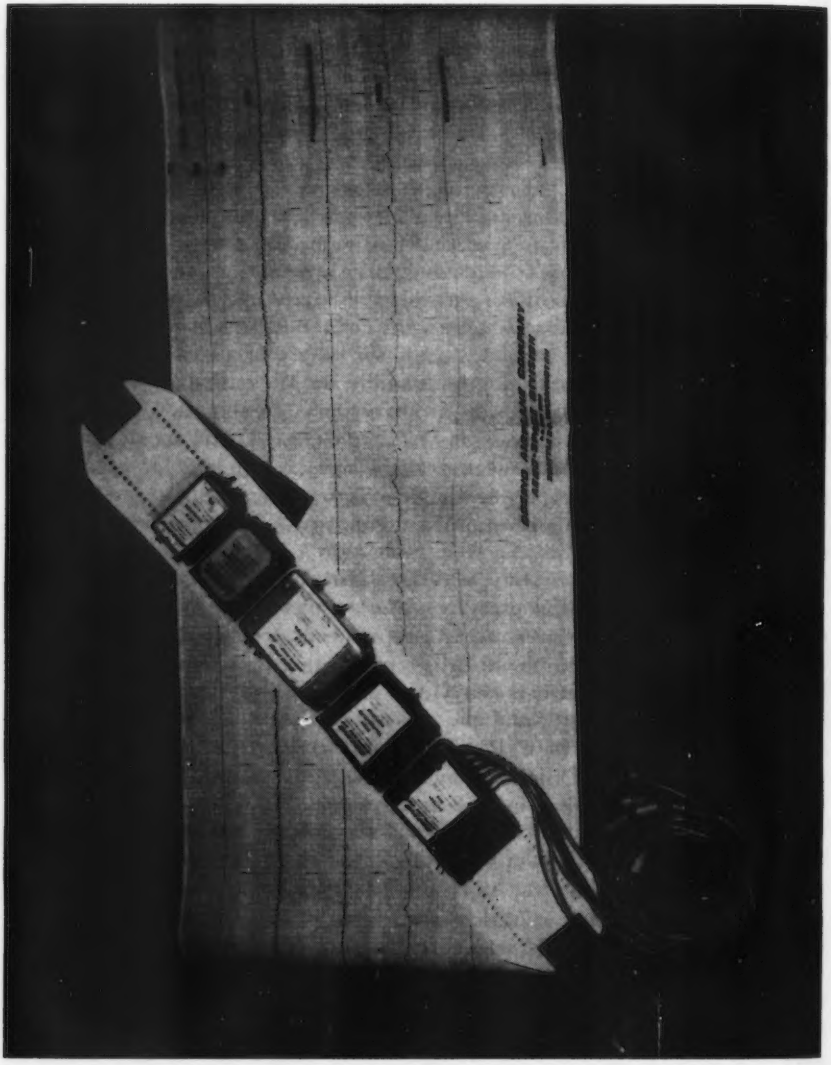

FIGURE 1. Miniature physiological recording instruments developed by the Boeing Airplane Co., producing the five channel simultaneous recording of EEG, ECG, respiration, body temperature, and phonocardiograph.

flight involving combinations of heat, acceleration, vibration, and other physical parameters may lead to a resultant O_2 lack which has similar physiological effects to simple hypoxia. Such problems are being evaluated at this time. Many facets are associated with the problem of maintaining an appropriate

environment to sustain man during space flight such as adequate humidity, carbon dioxide content, temperature, control of cabin toxicities, odours, etc. These facets play an equally important factor with the simple oxygen partial pressure of the sealed cabin or pressure suit for adequate insurance against hypoxia.

We should mention yet another aspect associated with this problem of hypoxia in space flight. Miniaturized electronic instrumentation is a most important aspect of both the cabin hardware and the physiological well being of the man. We could discuss the instrumentation in two main areas; namely, the *cabin sensors* and the *physiological instrumentation*. The telemetred data from both areas will be combined at the flight controller's desk giving essential information regarding the physical and physiological status during the flight. Cabin sensors refer to the miniature indicators which continually monitor the partial pressure of oxygen, the partial pressure of carbon dioxide, the temperature, the ambient pressure, vibration, and so on; and as the sophistication of the vehicle increases, these will monitor the toxicities present in the cabin environment through the use of a miniaturized mass spectograph. The second area, miniaturized physiological instruments, continually monitor the astronaut during all phases of the flight. The principal instruments are the respirometer, the electrocardiograph, the body temperature recorder, the automatic blood pressure recorder, the phonocardiograph, and the electroencephalograph.

The ageless problem of hypoxia will be an area of prime importance to the astronaut during space exploration. The combined engineering and biological aspects of the environment surrounding the man will require constant monitoring to insure that man is adequately protected and sustained in order to efficiently carry out his duties during space flight.

AN ANAESTHETIC SPRAY

A. W. CONN, M.D., F.R.C.P.(C)*

IN PAEDIATRIC ANAESTHESIA, topical anaesthesia is mainly confined to the larynx and trachea and usually precedes intubation. As spraying is usually performed during a period of apnoea, the time available is limited. Experience with various sprays has indicated the need for two features:

(1) A metal barrel and a nozzle of a somewhat large bore. The metal barrel enables the spray to be directed accurately despite anatomical difficulties. The large bore nozzle is less prone to blockage and enables an adequate amount of agent to be delivered with two or three sprays. Two difference tubes are supplied for straight and curved laryngoscope blades;

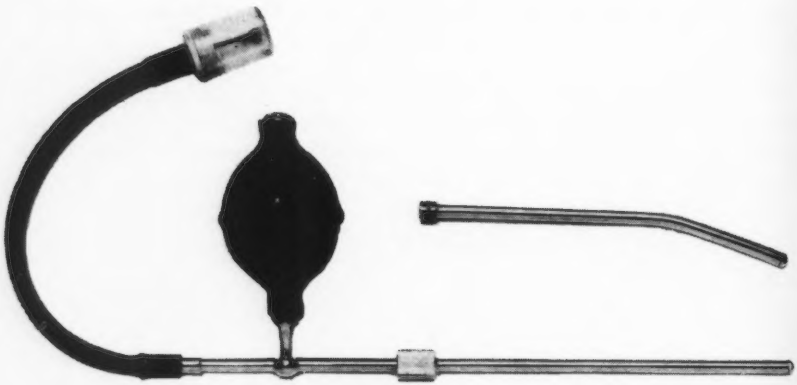

FIGURE 1. Anaesthetic Spray.

(2) Ease of maintenance and spare parts. The apparatus can be totally dismantled and repaired within minutes. Perishable parts have been reduced to a minimum. The rubber bulb is a standard B.P. bulb and polyethylene and rubber tubing are readily available.

With these considerations in mind, a spray was designed as illustrated†. Sprays similar to these have been in constant and satisfactory use for several years.

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†Available from Down Bros. and Mayer & Phelps Ltd., 70 Grenville Street, Toronto, Canada.

A FEW SUGGESTIONS TO THOSE WHO ARE GOING TO SURGERY (SUBJECT TO THE SURGEON'S APPROVAL)

LUCIEN RINFRET, M.D.*

IF YOU MUST undergo an operation, you will be wise to get prepared many days, even many weeks, ahead.

Let me suggest the few following points, which will help you, while being of assistance to your surgeon and your anaesthetist; by means of these you should be detoxified and decongested; you will bleed far less and, being relaxed, will need a smaller quantity of sedatives.

1. *Diet.* Salt and fat free; keep away from all fried food, especially fats and sugars, because frying makes them toxic; eat large quantities of fruits and vegetables, preferably raw (vitamins and mineral salts); also eat plenty of broiled or boiled meat (proteins).

2. *Rest and Relaxation.* Early to bed. Take care of physical and intellectual exhaustion. Refer solution of your problems to a later date, and so avoid stress.

3. *Physical Exercise and Fresh Air.* You MUST learn how to practise effective respiratory and limb exercises; it is of the utmost importance that they be done after the operation; decide now, in advance, to submit to this rule; you will have to get up from bed very soon (generally on the very day of the operation). Oxygen and muscular tone play an important role in surgery.

4. *Purgatives.* Except if surgery is to involve the digestive tract, the stomach, or the gall-bladder, drink a lot of water, fruit-juices, infusions of herbs.

5. *See your Doctor* for a physical examination, if possible before entering the hospital. This ought to avoid some hospital expenses and prevent certain delays, in case you might need preoperative medical treatment. This procedure should help, also, to ease the problem of shortgae of beds in the medical department.

6. *Look for Blood-Donors* amongst your relatives and friends, because you may have a need of transfusions.

7. *Make sure that the person* who is responsible for you will sign, when you enter the hospital.

8. *Don't forget to tell the doctors* and nurses if you are allergic, diabetic, or if you take cortisone.

9. *Have Confidence!*

"Your Anaesthetist"

*La Misericorde, Bellevue, and Jefferey-Hale's Hospitals, Quebec City.

QUELQUES CONSEILS AUX FUTURS OPÉRÉS, SUJETS À L'APPROBATION DU CHIRURGIEN

SI VOUS DEVEZ subir une opération, vous ferez bien de vous préparer plusieurs jours et même plusieurs semaines, à l'avance.

Je vous suggère les quelques conseils suivants, lesquels vous profiteront sûrement, tout en aidant votre chirurgien et votre anesthésiste; par ces moyens, vous serez désintoxiqué, décongestionné; aussi, vous saignerez moins et aurez besoin d'une quantité moindre de calmants, parce que détendu.

1. *Régime* sans sel et sans graisse: évitez les aliments frits de toute sorte, surtout les graisses et les sucres dénaturés; mangez beaucoup de fruits et légumes, crus de préférence (vitamines et sels minéraux) et des viandes maigres braisées ou bouillies (Protéines).
2. *Repos et détente.* Couchez-vous à bonne heure. Evitez le surmenage physique et intellectuel; remettez à plus tard la solution de vos problèmes (pour combattre le stress).
3. *Exercice Physique au grand air.* Apprenez à faire des exercices respiratoires et des exercices des membres; ils devront être pratiqués après l'opération, absolument; soyez donc bien décidé, à l'avance, à vous y soumettre; sachez, de plus, que vous devrez vous lever très vite, (le jour même de l'opération, en général). L'oxygène et la tonus musculaire jouent un grand rôle en chirurgie.
4. *Purgations*, excepté s'il est question d'une intervention sur le tube digestif, l'estomac ou la vésicule biliaire; buvez beaucoup d'eau, de jus de fruits, tisanes de queues de cerises.
5. *Faites-vous examiner* par votre médecin, au point de vue état général, si possible avant votre entrée à l'hôpital. Cela pourra vous évitez certains frais hospitaliers et une attente ennuyeuse, pour le cas où vous auriez besoin d'une préparation médicale. Cette façon de faire devrait aider, également, à régler le problème de pénurie de lits, dans les services de médecine.
6. *Trouvez des Donneurs de sang*, parmi vos parents et amis, au cas de besoin.
7. *Assurez-vous de la signature* de la personne responsable de vous, lors de votre entrée à l'hôpital.
8. *Avertissez* si vous êtes allergique, diabétique ou sous traitement à la cortisone.
9. *Ayez Confiance.*

"Votre anesthésiste"

BOOK REVIEWS

FUNDAMENTALS OF NERVE BLOCKING, By VINCENT J. COLLINS, M.S., M.D. Toronto: The Macmillan Company of Canada Ltd. 1960. $9.50.

THIS EXCELLENT LITTLE VOLUME is directed particularly to a discussion of the diagnostic and therapeutic uses of nerve blocking. Based as it is on the authority of the vast experience of the Pain Clinic at the Bellevue Hospital, it must be considered an important contribution to our literature. This reviewer would congratulate the author on avoiding the recent trend to preface his book with a text-book on anatomy.

Illustrations are excellent, and it is notable that a generous proportion of these are derived from other publications. Both the format and the language are clear and readable. This volume is highly recommended to anaesthetists, and this reviewer would hope that it might come to the attention of those physicians and surgeons who remain unaware of the benefits to their patients which may be derived from nerve blocking.

R.A.G.

ELECTROENCEPHALOGRAPHY IN ANESTHESIOLOGY. By ALBERT FAULCONER, M.D., M.S., and REGINALD G. BICKFORD, M.B., CH.B., M.R.C.P. Springfield, Ill.: Thomas (Toronto: The Ryerson Press). $5.25.

THIS 77-page account of a subject, previously poorly understood by the average anaesthetist, will be a welcome addition to his library. As a primer for the post-graduate student this book is probably unparallelled. The origin of the electrical potentials measured, the principles of the equipment involved, the effects of the commonly used anaesthetic agents and of various physiological changes are all discussed in turn. This is a very readable monograph which is to be recommended.

H.B.F.

GENERAL ANAESTHESIA FOR DENTAL SURGERY. By R. S. WALSH, F.F.A.R.C.S. Montreal: J. B. Lippincott Company. $3.75.

"IN SO FAR as the essential details of what is primarily a practical art can be conveyed in print it seems that Dr. Walsh has covered the ground." This quotation from the forward to this 94-page book expresses the scope of it, for here is a great deal of information about dental anaesthesia but still the art must be acquired by practise. This is a demanding form of anaesthesia where prompt decisions and action are required.

The statement that "hypoxia of greater or less severity accompanies every dental 'gas' " is plainly made, but in the final paragraphs two new methods of administering nitrous oxide are described, entitled analgesia and pre-oxygenation, which provide adequate oxygen. The chapters on the resistant

patient and complications should be of particular interest to the occasional dental anaesthetist, who in his own experience may rarely meet the described situation, but would benefit by knowledge of it.

This is a very readable book from which much practical information is available for anaesthesia for oral operations.

S.A.F.

EXPOSES D'ANESTHESIOLOGIE. Par P. HUGUENARD et P. JAQUENOUD. Paris: Masson et Cie. 1960.

L'OUVRAGE "Exposés d'Anesthésiologie," publié en deux tomes par P. Huguenard et P. Jaquenod, est susceptible de rendre service au praticien et à l'étudiant anesthésiste; au premier, il rappelle certaines notions essentielles de pharmacologie et de physiologie; au second, il fournit un enseignement pratique en vue de son certificat comme spécialiste.

La première série offre d'abord un glossaire qui définit et explique de façon précise un grand nombre de termes couramment utilisés an anesthésiologie, ainsi qu'une liste des synonymes usuels.

Le chapitre de la "consultation écrite," où l'élève prend connaissance du patient et rédige ses notes personnelles, est particulièrement intéressant. Les auteurs étudient aussi l'aspect pharmacologique de quelques anesthésiques: l'éther-diéthylique, l'éther divinylique, le pentothal. Les myorésolutifs, *i.e.* la d-tubercurarine et la succinylcholine, y sont traités avec beaucoup d'attention: définition, classification, propriétés physiologiques, posologie. Une mention spéciale est réservée aux ganglioplégiques, au métabolisme des hydrates de carbone et à l'ion potassium en anesthésie. Les auteurs présentent également une technique simple d'intubation avec images à l'appui.

La seconde série traite des problèmes suivants, souvent posés à l'anesthésiologiste: chirurgie du nouveau-né, du vieillard et de l'alcoolique; état de choc et complications pulmonaires; la première série mentionne, en outre, la chirurgie du malade neurologique, du brûlé grave, du diabétigue, la chirurgie abdominale d'urgence.

Il y a aussi un chapitre consacré aux sympathicomimétiques, aux dérivés de la belladone, aux opiacés, aux substituts du plasma et aux anesthésiques halogénés.

La douleur, le réveil, les hormones cortico-surrénaliennes, la maladie opératoire, la mécanique ventilatoire sont autant de sujets présentés ici avec beaucoup d'intérêt.

Les auteurs terminent par quelques notes de technique très instructives: la trachéotomie et les appareils de ventilation artificielle.

Le présent manuel s'avère très profitable, à notre avis, pour celui qui possède déjà des connaissances de base sur la spécialité; c'est en somme une excellente revue pharmacologique et physiologique. Il serait souhaitable cependant que les auteurs y ajoutent un troisième tome consacré aux questions de chimie, de biologie, d'anatomie, de physique et aux méthodes expérimentales qui ressortissent à l'anesthésiologie.

RENÉ LEBEAU, M.D.

BRITISH OXYGEN CANADA PRIZE

BRITISH OXYGEN CANADA LIMITED have made available the sum of $1,000 annually for a prize to be awarded by the Canadian Anaesthetists' Society for the best original work in Anaesthesia completed in Canada during the year preceding the award. The first such prize will be awarded at the time of the Annual Meeting of the Canadian Anaesthetists' Society in 1961. The following regulations apply:

Qualifications

(1) Applicant must be a resident in training in Anaesthesia or a practising anaesthetist.
(2) The study must be carried out in a Canadian Hospital or University, and must have been completed during the previous 12 months.
(3) The study submitted may be of a basic or clinical nature.

Submission and Selection

(1) Applicant's study is to be submitted in quadruplicate to the Secretary, Canadian Anaesthetists' Society, prior to April 1.
(2) Three (3) referees will be appointed by the Executive of the Canadian Anaesthetists' Society from departments of Anaesthesia in Canadian Universities. Not more than one referee shall be chosen from any one University.
(3) The prize-winning report or reports shall be presented at the Annual Meeting of the Canadian Anaesthetists' Society at which the award will be made, and will be subject to exclusive publication in the Canadian Anaesthetists' Society Journal. The right of publication of all reports submitted in application for the prize is reserved to the Canadian Anaesthetists' Society Journal subject to acceptance by the Editor.
(4) In the event of two (2) applicants submitting work judged by the referees to be of equal merit, the award may be divided at the discretion of the referees.
(5) If in the opinion of the referees the studies submitted do not warrant the award being made in any year, the prize will be deferred.

NEWS LETTER

THE COUNCIL of the Canadian Anaesthetists' Society has accepted an offer by British Oxygen Canada Limited of an annual sum to be given as a prize or prizes for the best original work in Anaesthesia in Canada during the year. The award will be known as The British Oxygen Canada Prize. Detailed announcements will be found elsewhere in this Journal.

ONTARIO DIVISION

The University of Toronto has announced the establishment of a three-year Diploma Course in Anaesthesia, commencing with the 1961-62 Academic Session. The Diploma will be awarded on the basis of examinations to be held in each year of the course.

The second Harry J. Shields Lecture in the University of Toronto was given by Dr. John Gillies of Edinburgh on September 9, 1960. Dr. Gillies' subject was "Clinical Medicine and Surgery in Anaesthetic Practice."

Dr. Robert Horne has been appointed to the staff of the Department of Anaesthesia, Queen's University, and the Kingston General Hospital.

QUEBEC DIVISION

Some one hundred anaesthetists, on their way to Toronto to attend the World Congress, spent September 2-3 in Montreal, where they were officially welcomed by the Mayor of Montreal, Senator Sarto Fournier, at an evening reception tendered by the City.

His Worship was thanked, in inimitable style, by Dr. Harold Griffith, to whom a delightful banquet was given on the following night by the Quebec Division of the Society, whose members also presented to Dr. Griffith a silver cigar box, in recognition of his contribution to the "boundless realm" of world-wide Anaesthesia.

Many of the distinguished delegates signed the Golden Book of the City of Montreal during their stay, and, with their wives and families, took cheerful advantage of the opportunity to tour not only the two great universities, but the Laurentians and historic sites in the older part of the City as well.

The anaesthetists of Montreal were particularly pleased to have had the opportunity of exposing our visitors to the many attractions of the metropolis, and the thanks of all are particularly merited by Dr. Leon Longtin and his committee, who were in charge of the arrangements.

The third annual McGill revision and refresher course in anaesthesia for those sitting examinations and General Practitioners engaged in anaesthesia was given by the staff of the Department of Anaesthesia and guests from the

Faculty of Medicine during the week of September 19-24, 1960. Approximately fifty doctors from many parts of Canada and the United States attended thirty-seven lectures and demonstrations on topics of current interest in the fields of basic science and their integration with clinical problems.

Dr. M. Digby Leigh, Associate Professor of Surgery (Anesthesia), University of Southern California and Director, Department of Anesthesia, Children's Hospital of Los Angeles, spent the last week of September in visitng old stamping grounds in Montreal. Dr. Leigh visited the Montreal Children's Hospital, where he was formerly director of Anaesthesia, as well as other teaching hospitals of McGill and the Univérsité de Montréal. He addressed the regular Monday night conclave of Montreal anaesthetists and, with Mrs. Leigh, regaled many of his old friends, including Dr. Wesley Bourne and Dr. Harold Griffith, at a dinner given in his honour by Dr. R. G. B. Gilbert.

Forrest Bird, Ph.D., was the principal speaker at a two-day seminar on "The Dialectics of Pressure Breathing," sponsored by the Department of Anaesthesia of McGill University on October 16 and 17.

The McGill Anaesthesia Programme for the year 1960-61 includes such well-known guest speakers as Drs. Digby M. Leigh, S. M. Campbell, Stuart Vandewater, George J. Thomas, David M. Little, and Merel M. Harmel. Copies of the full programme may still be had on application to the Chairman of the Department, Dr. R. G. B. Gilbert, 3801 University Street, Montreal 2, P.Q.

Division du Québec

A la mémoire du Docteur Gérard Lafortune, anesthésiologue. Le docteur Gérard Lafortune était anesthésiste à l'Hôpital St-Luc depuis le 12 mai 1953, année de sa certification en anesthésiologie. Le Docteur Lafortune nous quittait subitement le 26 septembre 1960 à l'âge de 38 ans.

Nous rendons hommage à son intégrité professionnelle qui concourut à faire connaître et aimer notre spécialité.

A son épouse et aux siens, assurance de notre sympathie la plus sincère.

En rapport avec le Deuxième Congrès Mondial des Anesthésistes. Le Docteur Eugène Allard recevait à Québec le 1er septembre 1960 la délégation d'expression française.

Les 2 et 3 septembre, le comité de réception montréalais, présidé par le Docteur Léon Longtin, recevait officiellement les délégués du Congrès aux Universités de Montréal et McGill et ainsi qu'à l'Hôtel-de-Ville.

Le 3 septembre, avait lieu le banquet en l'honner du Docteur Harold Griffith et la présentation d'une bourse.

L'accueil torontois a été des plus cordial. Il est à noter la collaboration étroite des hôpitaux torontois avec l'organisation du Congrès.

Visiteur illustre à Montréal. Le Docteur Digby Leigh revenait au pays pour une visite officielle après pas moins de 15 ans d'absence. Lors de réunions

scientifiques et sociales, ses amis et confrères ont eu l'occasion de constater que son enthousiasme et son esprit d'organisation étaient toujours les mêmes. Nous espérons que ses visites se feront plus fréquentes.

Un lien sera établi entre lui et nous puisque le Docteur Paul Perron, résident à l'Hôtel-Dieu de Montréal, le rejoindra à Los Angeles pour une période de six mois à partir de janvier 1961.

Hôpital du Sacré-Coeur. Le Docteur Roger Gagnon annonçait, à la mi-septembre, l'ouverture à l'Hôpital du Sacré-Coeur de Cartierville d'une nouvelle salle de réveil avec appareillage électronique pour une surveillance plus étroite et plus suivie des malades en phase de recouvrance.

Nomination universitaire. Le Docteur Louis Lamoureux a été nommé, à l'aurore de la nouvelle année académique, professeur agrégé d'anesthésiologie à la Faculté de Médecine de l'Université de Montréal par le Conseil de la Faculté.

Alberta Division

The annual meeting of the Alberta Division of the Canadian Anaesthetists' Society was held at the Palliser Hotel, Calgary, September 30. This meeting was held in conjunction with the annual meeting of the Alberta Division of the Canadian Medical Association and the Alberta College of Physicians and Surgeons. After the meeting the Calgary Anaesthetists' Society was host to the Division members and their wives at the home of Dr. and Mrs. N. E. Foster.

There have been several changes of staff at the Calgary hospitals.

Dr. W. M. Jones has returned to Toronto and is now practising at the Toronto Western Hospital.

Dr. Alan M. Keil has joined the staff of the Holy Cross Hospital. He comes from Britain via University Hospital, Saskatoon.

Dr. Harry Donaldson has returned to Calgary General Hospital after two years at University Hospital, Saskatoon.

Dr. Murray Tanasichuk has joined the staff ot Calgary General Hospital from Minneapolis and St. Boniface.

Dr. Walter Mudry, who has been doing anaesthesia as well as General Practice in Calgary for several years is now a resident in Anaesthesia at the Calgary General.

A new 600 bed Royal Alexandra Hospital is to be built in Edmonton.

Dr. R. J. Stewart formerly of Vancouver and Calgary has joined the staff at the Royal Alexandra Hospital, Edmonton.

Dr. Wm. Cochrane from Rochester, N.Y., and Liverpool, England, is also now on the staff of the Royal Alexandra Hospital.

At the University Hospital, Edmonton, there is a new service wing which includes an operating room suite.

Dr. Zella Hoar, a former staff member of The University Hospital in Edmonton has resumed practice.

Dr. Martin Hagen has joined the staff of The University Hospital, Edmonton, as a clinical assistant.

Dr. Frank Haley who trained at the University of Alberta and University of Saskatchewan Hospitals is Director of Research and Clinical Investigation in the Department of Anaesthesia of the Faculty of Medicine, University of Alberta.

There is a new six-storey addition to the Medical Building of the University of Alberta. One floor of this building is to be used for animal research under the clinical departments of the Faculty of Medicine.

Saskatchewan Division

Dr. G. W. Kinsman has limited his practice to full-time anaesthesia beginning October 1, 1960.

Manitoba Division

In April 1959, the Manitoba Society of Medical Hypnosis was formed. Among the founding members were the following Winnipeg Anaesthetists: Dr. P. McGarry of Grace Hospital, Dr. S. Kantor of Misercordia Hospital, and Dr. R. S. Lambie of St. Boniface Hospital. Dr. G. Semelka of St. Boniface Hospital has since become an active member of this group.

Dr. S. Luginsky, Chief Anaesthetist at the Grace Hospital, Winnipeg, has resigned his post to take up residence in the Los Angeles area.

Dr. Max Sadove was the guest speaker at the opening meeting of the Manitoba Division of the Canadian Anaesthetists' Society held at the Victoria General Hospital on September 27, 1960.

The annual meeting of the Western Division of the Canadian Anaesthetists' Society is to be held in Winnipeg on March 8, 9, 10, and 11. An interesting programme featuring the themes "Shock" and "Pulmonary Diseases and Anaesthesia" is planned. Guest speakers will include Drs. S. Hersey of New York, M. Nickerson of the Department of Pharmacology at the University of Manitoba, A. Thomson and R. Cherniak of the Department of Physiology at the University of Manitoba, and R. A. Gordon, of Toronto.

Dr. J. Brenner, Head of the Department of Anaesthesia at the Misercordia Hospital for many years, has been absent from the hospital for several months due to ill health.

UNIVERSITIES ANNOUNCE DIPLOMA COURSES IN ANAESTHESIA

University of Toronto

The University of Toronto has announced the inauguration of a Diploma Course in Anaesthesia, to commence July 1, 1961. This is a three-year academic course to be given by the Department of Anaesthesia under the post-graduate division of the Faculty of Medicine. The course will be given in association with resident clinical appointments in the teaching hospitals associated with the University of Toronto. The diploma in anaesthetics will be awarded by the University on satisfactory completion of the three-year course, subject to success in the examinations at the end of each of the three years.

Applications should be forwarded to:

Professor S. M. Campbell,
Department of Anaesthesia,
c/o Toronto General Hospital,
Toronto, Ontario, Canada.

Queen's University

The Department of Anaesthesia of Queen's University, Kingston, announces the inauguration of a post-graduate diploma course. All phases of training, including appointments in Clinical Anaesthesia, Internal Medicine, and the Basic Sciences, will be offered to suitable candidates who are desirous of obtaining higher qualifications in the specialty of Anaesthesia. The post-graduate students who satisfactorily complete three years of training, one of which shall be spent either in Internal Medicine or a Basic Science, shall be eligible for the examination for the diploma in Anaesthesia granted by the University. The post-graduate course also satisfies the requirements for examination for the Certificate and Fellowship of the Royal College of Physicians and Surgeons of Canada.

Appointments are limited and will commence on July 1 of each year. Applications should be submitted at least nine months in advance, and will be reviewed on a competitive basis. Preference will be shown to graduates of Canadian and Commonwealth Universities, and to those foreign medical graduates holding the E.C.F.M.G. Certificate and intending to return to their native country on completion of their training. Intern appointments of one to three years are available at the General Hospital and the Hôtel Dieu Hospital in Kingston, offering a wide variety of clinical experience in association with all surgical specialties.

Teaching is done on the tutorial plan by members of the Department of Anaesthesia, with emphasis on the Basic Sciences as applied to Anaesthesia. In addition there are biannual courses in Applied Anatomy and Pathology, and weekly clinical conferences.

Applications should be forwarded to:

S. L. Vandewater, M.D., F.R.C.P.(C),
Professor of Anaesthesia,
Queen's University,
Kingston, Ontario, Canada.

MEETINGS

CANADIAN ANAESTHETISTS' SOCIETY, WESTERN DIVISIONS
Winnipeg, Manitoba.
March 8-11, 1961

CANADIAN ANAESTHETISTS' SOCIETY, ANNUAL GENERAL MEETING
Seigniory Club, Montebello, P.Q.
May 15-18, 1961

INTERNATIONAL ANESTHESIA RESEARCH SOCIETY, ANNUAL CONGRESS
Shamrock Hotel, Houston, Texas
April 9-13, 1961

BIENNIAL WESTERN CONFERENCE ON ANESTHESIOLOGY
Sheraton Hotel, Portland, Oregon
May 16-18, 1961